"Stability is an absolutely universal attribute of nature and therefore it has to be reflected in the basis laws of nature. If the knowledge can be constructed on the basis of small perturbations then scientific thinking could be based on some type of Lyapunov function. In any case this function always exists from postulate of stability."

Chetaev, 1936

University of Alberta

Mathematical Studies of the Transmission Dynamics of Infectious Diseases in Heterogenous Populations

by

Hongbin Guo

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Abstract

Part 1 of this thesis contains our contribution to mathematical methodology. We introduce a new approach to the method of global Lyapunov functions using graph theory, and demonstrate the approach through two heterogenous epidemic models: a multi-group SEIR model and a multi-stage model. The uniqueness and global stability of endemic equilibria of the n-group SEIR model has been a well-known open problem in mathematical epidemiology. This open problem is completely resolved in the thesis (Theorem 2.3, p36) for the first time. More and more research activities in mathematical epidemiology are directed at heterogeneity in disease transmission dynamics. We expect that the graph-theoretical approach described in the thesis will see a much wider range of applications.

In Part 2, we investigate the transmission dynamics of tuberculosis (TB) using mathematical models. TB is an old infectious disease that saw an alarming global resurgence since the 1990s. Many factors have contributed to the comeback of TB and they have been well studied in the literature. In this thesis, we focus on the issue of global spread of TB through population migration, and investigate the impact of the immigration from developing countries on the TB incidence of developed countries. We propose a multi-group model to investigate the TB transmission dynamics among a population in a high TB incidence country, a population of immigrants and a local-born population in a developed country. Such a model is new in the literature, and the global dynamics are completely established (Theorem 5.3).

We carry out two case studies using our model to analyze TB data from Canada and the UK. We demonstrate that the cross-infection from immigrants to local-born can be a significant factor for the TB incidence in the local-born population. The effects of such a cross-infection may not be obvious when the TB incidence among the immigrants is low, as in the case of Canada. However, we show that, if the TB incidence among immigrants is sufficiently high, as in the case of the UK, the cross-infection can significantly change the TB trend in the local-born population. Our analysis on the recent TB trend in the UK confirms a hypothesis raised in a UK government TB report [64]. Impact of other important factors on the TB dynamics such as latency and loss of immunity are also investigated in the thesis.

To my parents

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Chapter 0. Introduction and Thesis Summary

The impact of infectious diseases on human, animal and wildlife is enormous, both in terms of suffering and in terms of social and economic consequences. From well-known diseases like plague, cholera, tuberculosis, pneumonia, gonorrhea, smallpox, malaria, measles to recent West Nile virus (1937), Lyme disease (1975), HIV/AIDS (1981), hepatitis C (1989), hepatitis E (1990), avian influenza(1990s), hantavirus (1993), SARS (2003) etc, there are no exceptions that they caused huge morbidity and mortality. Although great advances have been made in vaccination and medical treatment since the last century, emerging and reemerging infectious diseases still present an increasing risk on a global scale, see [2, 17, 69].

According to the transmission agents of infectious diseases there are several classes of transmission types [2]. One is that diseases are transmitted by viruses, such as influenza, measles, rubella, chickenpox, usually conferring immunity against reinfection. Another is that diseases are transmitted by bacteria, such as tuberculosis, meningitis and gonorrhea, conferring no immunity against reinfection. Other agents are protozoa, helminths and prions [69]. It is evident that prions are the main causes of bovine spongiform encephalopathy (BSE), Creutzfeldt-Jakob disease (CJD). A more severe situation now facing humans is that the infectious diseases are transmitted from animals to humans. SARS, avian influenza and monkeypox have jumped from animals into human populations. This led to a great challenge in understanding and controlling infectious diseases. The following graph provides an illustration of cross-interactions among human, wildlife and domestic animals diseases (see Figure 0.1).

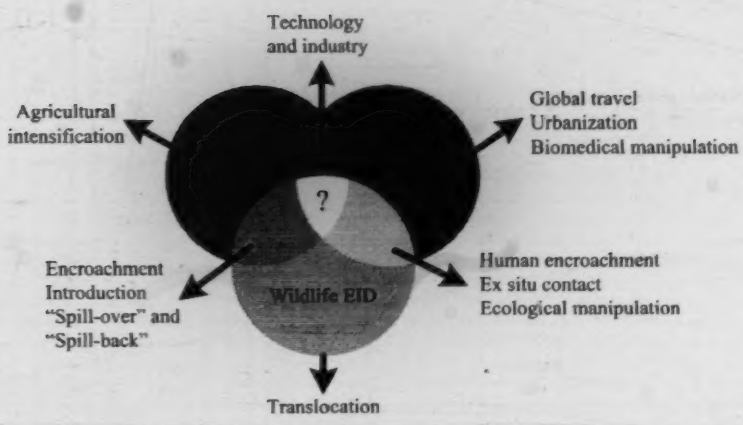


Figure 0.1: Interactions between human, wildlife and domestic animals emerging infectious diseases (EID). Source: Daszak et al Science 2000.

0.1 Mathematical epidemiology

Mathematical epidemiology concerns with modeling the spread of infectious diseases in host populations. One of main goals of mathematical epidemiology is to understand how to control and eradicate diseases.

Earlier in the 18th century, Daniel Bernoulli made one of the first mathematical contributions to infectious diseases control by developing a model of smallpox [11, 69, 109]. Since Bernoulli, more and more mathematicians and scientists have joined in and offered many practical insights into infectious diseases control. The first contribution to modern mathematical epidemiology are due to P. D. En'ko between 1873 and 1894 [38]. In 1906, Hamer developed a discrete model to study the recurrence of measles and mass-action principle was introduced for the first time [61, 109]. Ross in 1911 formulated a differential equation model of malaria [69]. Beginning in 1927, Kermack and McKendrick studied compartmental models of disease transmission in their three famous papers and they first derived out the well-known threshold behavior for epidemic models that the density of susceptibles must exceed a critical value in order for an epidemic outbreak to occur [69, 82].

Since the Kermack and McKendrick's deterministic compartmental models of communicable diseases described by ordinary differential equations (ODEs), the mathematical tools used in epidemiology modeling have evolved into a more broad field

of mathematics. The models described by ODEs usually assume that the time spent in compartment is exponentially distributed. For many diseases, hosts spend a fixed time in a compartment. This gives rise to a differential-difference equation model. Moreover, an arbitrary distribution can be assumed of time spent in a compartment, leading to integral equation or integro-differential equations [17]. Epidemiological models with spatial structures have been used to describe the spatial heterogeneity and the spatial spread of infectious diseases by diffusion-type partial differential equations (PDEs). One of such examples is the study of fox rabies [2, 69]. Spatial models with dispersal-kernels are formulated by integral equations with kernels describing daily contacts of infectives with their neighbors. Described often by integral-differential equations, age-structured epidemiology models with either continuous age or discrete age groups are used to model the age-related mixing behaviors of infectious diseases such as measles and HIV/AIDS (see survey paper [69]).

In contrast with deterministic epidemic models, stochastic epidemic models including, discrete time, continuous time Markov chain models and stochastic differential equation models are brought forward in the last several decades [5]. Other related methods have chain binomial epidemic processes and branching epidemic processes [1]. Stochastic models are generally more difficult to analyze than their deterministic counterparts. A more detailed discussion on the advantages and limitations of different types of epidemic models is given in [71].

More recently, a new strategy of modeling heterogeneity of contact patterns of infectiousness, contact network epidemiology appeared with ideas different from conventional methods. In modeling more complex contact patterns of infectious diseases, new strategy is based on contact network involving with the ideas from graph theory (see survey paper [109]).

For many infectious diseases, the epidemic models can be very complicated and this usually leads to the study of mathematical models with heterogeneous features. Heterogeneity exists in many aspects of disease transmission processes: heterogeneous spatial distribution of host populations; heterogeneous susceptibility among age groups, heterogeneous social behaviors among groups for sexually transmitted diseases, and multi-hosts for many diseases such as West Nile virus and Avian flu. Heterogeneity produces complexity in the transmission processes of diseases. It has been a prime subject of mathematical modeling in the past two decades, and the research has

intensified in recent years. Due to the extremely large scales of the resulting models, rigorously establishing their global dynamics poses a great mathematical challenge.

Mathematical modeling is an important tool in studying a diverse range of infectious diseases, and has proven successful in investigating disease transmission dynamics to gain better qualitative and quantitative understanding of the mechanisms of disease transmission processes. Such an improved understanding can help public health authorities to make more reliable predictions and to better evaluate disease prevention and control strategies (see [69, 2] for details).

In this thesis we deal with the transmission dynamics of infectious diseases in heterogeneous populations described by deterministic models using ordinary differential equations.

0.2 Compartmental models

The spread of infectious diseases in a population can be described mathematically using compartmental models. Disease transmission is a dynamical process driven by the interaction between the susceptible and the infective. In compartmental models, the total population is divided into distinct compartments according to the disease status such as susceptible (S), exposed (latent) (E), infectious (I) and recovered (R) compartments, as shown in Figure 0.2. The total host population is $N = S+E+I+R$. All newborns or immigrants are assumed to be susceptible. When there is an adequate contact between a susceptible and an infective so that transmission occurs, then the susceptible enters the exposed class with a waiting time – latent period. After the latent period ends, the individual enters the class of infectives, who are infectious in the sense that they are capable of transmitting the infection. When the infection period ends, the individual enters the recovered class with permanent or temporary immunity [68, 69].

The transfer terms $\epsilon E, \gamma I, \delta R$, correspond to exponentially distributed waiting times in the corresponding compartments. So, $1/\epsilon$ is the mean latent period, $1/\gamma$ is the mean infectious period, $1/\delta$ is the mean immune period. The recruitment term of births or immigration π maybe be either a constant or a function of total population. The natural death or emigration appears in all groups and an extra death rate is necessary if the disease is death-related.

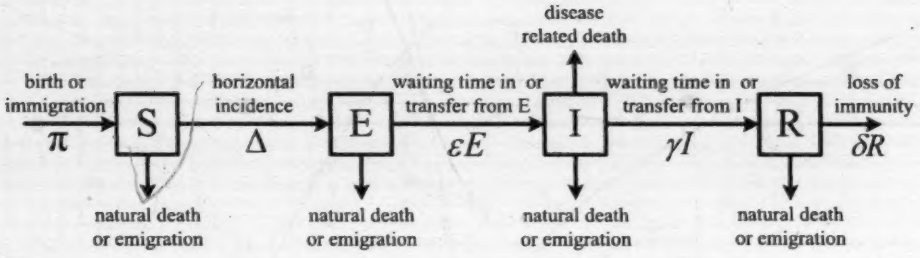


Figure 0.2: Flow diagram of an SEIR model.

The horizontal incidence term Δ is the infection rate of susceptible individuals through their contacts with infectives. Two commonly used incidence forms are simple mass action form, βSI, also called bilinear incidence, and standard incidence form, $\beta SI/N$, also called proportionate mixing incidence. If β is the average number of adequate contacts (i.e., contacts sufficient for transmission) of a person per unit time, then $\beta I/N$ is the average number of contacts with infectives per unit time of one susceptible, and $(\beta I/N)S$ is the number of new cases per unit time due to the S susceptibles. This formulation leads to standard incidence forms [69]. For simple mass action law βSI, it is assumed that the average number of contacts capable of transmitting the disease that an individual makes with infectious individuals per unit time, is proportional to the number of infectives. Here β reflects the likelihood that an infectious case will successfully transmit the infection to a susceptible individual. For the difference between these two incidence forms, we refer the reader to [68, 69, 106].

Based on this basic SEIR model and flow patterns between different compartments, many other related models can be derived out such as SEIRS, SEI, SEIS, SIR, SIRS, SIS, SI models depending on the characteristics of the particular disease being modeled and the purpose of the model. For example, SEIRS model is suitable for influenza and SEIR model for measles.

Many possible forms of the incidence, demographic structures and epidemiological-demographic interactions can be added into the epidemic models. So the epidemiological compartment structures vary from very simple to quite complicated. For instance, the epidemic models can include vertical transmission, age-dependent or age-specific disease transmission, infection class age, variable infectivity, cross immunity, intercohort transmission, short infectious period, optimal vaccination patterns, heterogeneity and structured mixing etc (see survey paper [5, 69]).

0.3 Threshold - the basic reproduction number

A primary goal of public heath is to bring disease from above an epidemic threshold value to below the threshold value, thereby eliminating the threat of a large-scale epidemic. This can be achieved through interventions that either directly impact the transmission of the pathogen (transmission reducing), modify patterns of interaction so that the pathogen can not easily spread through the population (contact reducing), or immunization segments of the population (immunizing) [109].

The threshold for many deterministic epidemiological models is the basic reproduction number, which is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible [2]. The basic reproduction number is also called the basic reproduction ratio denoted by R_0. An infection can start in a fully susceptible population if and only if the R_0 is greater than one. In this sense, the basic reproduction number is often considered as the threshold quantity which determines when an infection can invade and persist in a new host population. A detailed explanation can be found in [2, 69, 135].

In Section 0.2, we consider a standard SEIR model with bilinear incidence rate βSI, constant birth rate π and death rate d. The model has the basic reproduction number

$$R_0 = \beta \cdot \frac{\epsilon}{d+\epsilon} \cdot \frac{1}{d+\gamma},$$

where β is the average number of effective contacts by a single infective per unit time in an entirely susceptible population. The fraction $\epsilon/(d+\epsilon)$ is the probability of an infected to survive the latent period. The last part $1/(d+\gamma)$ is mean infectious period of individual in the infective class and alive. So for the SEIR model, if $R_0 > 1$, the disease will invade the population. If $R_0 < 1$, the disease will die out in the population. In other words, if $R_0 > 1$, then each infected individual will transmit disease to at least one other individual during the infectious period, and the model predicts that disease will spread through the population. If not, then the disease is expected to fizzle out before reaching a substantial fraction of the population. Thus R_0 is a critical epidemiological value. For most epidemic models, the threshold value exists and the following criteria is stated in [37].

Threshold Quantity: *The disease can invade population if $R_0 > 1$, while it can not if $R_0 < 1$.*

Threshold criteria says that if $R_0 > 1$, then the disease can invade in population and after a long time period, the infective individuals or the infective fraction in the whole population keeps constant. This situation is called endemic and in mathematical epidemiology it is described by endemic equilibrium. In contrast that if $R_0 < 1$, the disease can not invade in population. This means that all the infective individuals will be extinct and the whole population is susceptible; the disease dies out finally in the population.

While for some epidemic models with extra immigration fraction into latent class E or infectious class I, the threshold behavior doesn't exist [16, 104]. In the case of presence of backward bifurcation in the model, multiple equilibrium situations are possible and thus the disease can persist in the population even if $R_0 < 1$ [4, 54, 104, 134].

Mathematically, the basic reproduction number can be derived by several methods. The most general method is by linearization at the disease-free equilibrium, based on the local stability of disease-free equilibrium. Other ways are based on the existence of endemic equilibrium and local stability of endemic equilibrium. For many epidemic models of infectious diseases with features of heterogeneity such as multi-group transmission, multi-strain infectivity, proportionate mixing, age structure etc, the next generation operator approach has also been used to derive out the basic reproduction number, which is defined as the spectral radius of a next generation matrix that is related to the Jacobian matrix at the disease-free equilibrium. For the general theory and derivation of next generation matrix approach, we refer to [37, 135]. In Chapter 2 and Chapter 3, a similar way is used to find out the basic reproduction numbers for a class of multi-group models and a general class of multi-stage progression models.

Although it is worthy to note that threshold behavior determines not only when the local stability of the disease-free equilibrium switches, but also when the endemic equilibrium persists in the population, the global behavior of the disease-free equilibrium or endemic equilibrium requires further analysis to determine.

0.4 Global stability

Consider the nonlinear system

$$x' = f(x) \tag{0.1}$$

where $x \in E$, an open subset of $\mathbb{R}^n$ and $f : E \to \mathbb{R}^n$ is C^1. Let $x(t; x_0)$ be the solution to (0.1) satisfying the initial condition $x(0) = x_0$ and $\phi_t : E \to \mathbb{R}^n$ be the flow of (0.1) denoted by $\phi_t(x_0) = x(t; x_0)$. A point $\bar{x}$ is called an *equilibrium point* or *critical point* of (0.1) if $f(\bar{x}) = 0$. A point $p \in E$ is called an *ω-limit point* of $x(t; x_0)$ of (0.1) if there is a sequence $\{t_n\}$ such that $\lim_{n\to\infty} t_n = \infty$ and $\lim_{n\to\infty} x(t_n; x_0) = p$. All ω-limit points of the solution $x(t; x_0)$ is denoted by a set $\omega(x_0)$, which always tell the long-term behavior of the solution through x_0.

An equilibrium point $\bar{x} \in E$ of (0.1) is said to be *locally stable* or simply *stable* if, for each neighborhood U of $\bar{x}$, there exits a neighborhood V of $\bar{x}$ such that $x(t, V) \subset U$ for all $t > 0$. The local stability of an equilibrium point $\bar{x}$ can be routinely verified by definition or by linearizing (0.1) at $\bar{x}$ and using Routh-Hurwitz Criteria.

An equilibrium point $\bar{x} \in E$ of (0.1) is said to *attract* points in a neighborhood W if $x(t; x_0) \to \bar{x}$ as $t \to \infty$ for each $x_0 \in W$. An equilibrium point $\bar{x}$ is said to be *asymptotically stable* if it is stable and attracts a neighborhood. The *basin of attraction* of $\bar{x}$ is the union of all points which it attracts. An equilibrium point $\bar{x}$ is said to be *globally asymptotically stable* or simply *globally stable* with respect to an open set $D \subset \mathbb{R}^n$, if it is asymptotically stable and its basin of attraction contains D (see [94]). Note that if $\bar{x}$ is globally stable with respect to D, then $\bar{x}$ is necessarily the only equilibrium in D. The proof of global stability is nontrivial mathematically and difficult in practice.

In the study of epidemiology, an important aspect under consideration is to investigate the long-time behavior of the system. It is desirable to determine whether the disease goes to a steady state (disease-free or endemic), whether periodic oscillations appear or whether there is other behaviors [101]. So for the simple case, i.e., if $\omega(x_0) = \{p\}$, then ω-limit set contains only one equilibrium point p, then we can make a conclusion that the disease will eventually go to the steady state, at the same time, ruling out the existence of periodic behaviors.

There are several ways to rule out periodic solutions in the ω-limit set of the systems in the literature. The well-known *Poincaré-Bendixson's theorem* combined with *Bendixson's Criteria* or *Dulac's Criteria* are the classical results for the planar

systems [53, 116]. In [18], a new condition is proposed based on the application of Stokes theorem for 3-dimension system. Due to Hirsch [73], Smith[123] and Muldowney [111], the Bendixson's criteria was generalized to higher dimensions. This was further developed and the generalized Dulac Criteria are derived for higher dimensions systems in [90, 91, 94, 96]. This method is also called *Li and Muldowney* geometric approach and has been used to solve the global stability problems in several classes of epidemic models [54, 92, 93, 94, 95, 101, 104].

An alternative method, the Lyapunov second method dating back to the 1890s, is also commonly used in proving stability in high dimensional systems. In next section, we will introduce this method in detail.

0.5 Lyapunov functions

The Lyapunov second method have been a standard tool in the analysis of nonlinear differential equations and dynamical systems. The following definitions follow that in [116].

Let $f \in C^1(E), V \in C^1(E), E \subset \mathbb{R}^n$ be an open set and let ϕ_t denote the flow of the differential equation (0.1). Then, for $x \in E$, the derivative of the function $V(x)$ along the solution $\phi_t(x)$ is

$$\dot{V}(x) = \frac{d}{dt} V(\phi_t(x))|_{t=0} = \nabla V(x) \cdot f(x),$$

where $\nabla V(x)$ is the gradient of V. If $\dot{V}(x)$ is negative in E then $V(x)$ decreases along the solution $\phi_t(x_0)$ through $x_0 \in E$.

Lyapunov Theorem: *Let E be an open subset of $\mathbb{R}^n$ containing $\bar{x}$. Let $f \in C^1(E)$ and $f(\bar{x}) = 0$. Suppose there exists a real-valued function $V \in C^1(E)$ satisfying $V(\bar{x}) = 0$ and $V(x) > 0$ if $x \in E$ and $x \neq \bar{x}$. Then*

(i) If $\dot{V}(x) \leq 0$ for all $x \in E$, $\bar{x}$ is stable.

(ii) If $\dot{V}(x) < 0$ for all $x \in E - \{\bar{x}\}$, $\bar{x}$ is asymptotically stable.

(iii) If $\dot{V}(x) > 0$ for all $x \in E - \{\bar{x}\}$, $\bar{x}$ is unstable.

A function $V : \mathbb{R}^n \to \mathbb{R}$ satisfying hypothesis (1) of the above Lyapunov theorem is called a *Lyapunov function*. Lyapunov's theorem was further extended as the LaSalle's

Invariance Principle [89]: if this only requires $\dot{V} \leq 0$ in E, then all omega limit sets of (0.1) are contained in the maximal compact invariant subset K of $\{x \in E : \dot{V}(x) = 0\}$. In particular, if E is positively invariant and $K = \{\bar{x}\}$, then $x(t, x_0) \to \bar{x}$ as $t \to \infty$. We note that this also implies the local stability of $\bar{x}$, since otherwise K would contain a non-constant full orbit.

Global Lyapunov functions are extremely useful especially in n-dimensional systems (≥ 3) when they exist. It is known that Lyapunov functions are often difficult to construct since there are no general approaches for their construction.

Lotka-Volterra systems are widely studied in both ecology and other fields and many types of Lyapunov functions related are proposed (see review paper [118]). B. S. Goh in 1977 [51, 52] constructed a special form of global Lyapunov functions when studying global-stability problem for a generalized Lotka-Volterra systems [8]. Goh constructed the following Lyapunov function:

$$V(x) = \sum_{i=1}^{n} c_i \left(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*} \right), \tag{0.2}$$

where $x_i > 0$ is the i-th variable and $x_i^* > 0 (i = 1, \cdots, n)$ are positive constants and usually they are coordinates of equilibria. c_i are positive coefficients and can be determined by a linear system. Thus $V(x) > 0$ if $x \neq x^*$ and $V(x) = 0$ iff $x = x^*$. The time derivative along a solution of system (0.1) is

$$\dot{V}(x) = \sum_{i=1}^{n} c_i \left(1 - \frac{x_i^*}{x_i} \right) x_i'.$$

In compartmental epidemic models, x_i denotes the i-th disease status of host individual. x_i^* denotes the i-th component of the equilibrium point.

We remark that this class of global Lyapunov functions are very general and contains the Lyapunov function for global stability of disease-free equilibrium (DFE), $P_0 = (x_1, x_2, \cdots, x_n) = (1, 0, \cdots, 0)$. Substituting P_0 and $c_1 = 0$ into (0.2), we see that

$$V(P_0) = \sum_{i=2}^{n} c_i x_i$$

since $\lim_{x_i^* \to 0^+} x_i^* \ln x_i / x_i^* = 0$.

This Lyapunov function has been successfully and widely used in ecological models [48, 51, 52, 75] and epidemic models [8, 22]. It is named the *Volterra-Goh* Lyapunov

function (see [8] for more detail). For higher dimensional models, Goh, Capasso, Beretta etc used matrix theory to derive sufficient conditions for the global stability.

Recently, Lyapunov functions of this type were revisited (e.g. [85, 86]) and successfully applied to the study of several classes of epidemiological models [55, 56, 57, 58, 59].

In this thesis, we will further explore the potential of this important Lyapunov function. We have developed a graph-theoretical approach, which allows us to apply this Lyapunov function to several important classes of large-scale epidemic models, and completely resolve the global stability problem for endemic equilibrium for these models.

0.6 Thesis summary

The theme of the mathematical research in this thesis is the investigation of the transmission dynamics of infectious diseases in heterogenous host populations, using mathematical modeling. The thesis is divided into two parts. Part 1 is mathematical methodology. Part 2 is mathematical modeling of tuberculosis.

Lyapunov functions are widely used in modern theories of differential equations and dynamical systems. One reason is their easy application without much discussion and direct consequence of global stability for nonlinear systems. Due to the difficulty in constructing global Lyapunov functions, the application in high dimensional systems has many restrictions. Because of the increased complexity, the derivative of Lyapunov functions are quite complicated. Thus a general and unified method to deal with this difficulty for a large class of nonlinear systems is necessary. In Chapter 1, we introduce a new graph-theoretic approach to the method of global Lyapunov functions using graph theory and demonstrate in detail how our graph-theoretical approach can be used to completely resolve the global stability of endemic equilibria.

In Chapters 2 and 3, the graph-theoretical approach is demonstrated through two classes of large-scale heterogenous epidemic models: a multi-group SEIR model and a multi-stage (MS) model. For the first time, we completely prove the uniqueness and global stability of the endemic equilibria of the n-group SEIR models, which have been a well-known open problem in mathematical epidemiology. In the mean time, a complete framework of our graph-theoretical approach to the method of Lyapunov functions is

presented to be applied to prove the global stability of endemic equilibria for more complicated high-dimensional epidemic models. The multi-stage model is a generic generalization of several endemic models with multiple stages. The global stability of the endemic equilibria for a high-dimensional MS model with bilinear incidence is resolved for the first time.

In Chapter 4, a basic introduction of tuberculosis (TB) is given and previous mathematical compartmental modeling of tuberculosis is reviewed.

In Chapter 5, we focus on the global spread of TB through population migration from developing countries to developed countries to investigate the impact of the immigration from high TB incidence countries on the TB incidence rate of developed countries (low TB incidence country). We propose a multi-population model to investigate the TB transmission dynamics among three populations: a population in a high TB incidence country, a population of immigrants from high TB incidence countries and a local-born population within an immigration country. The global dynamics of the full model is completely established.

In Chapter 6, based on the 2-population model of TB transmission in an immigration country in Chapter 5, we investigate the impact of cross-infection from foreign-borns to local-borns on the TB incidence rate of local-born population, and the effect of new immigrants with latent TB on TB incidence rate of foreign-born population. Cases studies in two countries, Canada and the UK, are carried out using real TB data from these countries. Our simulation results establish that cross-infection from foreign-born population to local-born population plays a key role in the TB incidence of local-born population: when the TB incidence of the immigrant population is relatively low, as in the case of Canada, TB incidence in local-born population may maintain its declining trend; when the TB incidence in the immigrant population is sufficiently high, as is the case of the UK, the TB incidence in the local-born population remains constant, or even be on the rise. This result confirms a hypothesis in a government report from the UK.

Our studies provide an answer to a public health issue raised in earlier TB studies: should Canada continue to commit resources on TB screening of new immigrants, given that the TB problem in immigrant population has little impact on the TB incidence of Canadian-born population? Our studies in Chapter 6 show that the cross-infection from immigrants to local-born populations can not be ignored. If Canada is to loosen

the TB screening of new immigrants, especially those from high TB incidence countries, then the current scenario in the UK may happen in Canada: not only TB incidence in the immigrant population will shoot up, the TB incidence in the local-born population will change from declining to going steady, even to growing.

In Chapter 7, a four-dimensional TB model with new immigrants who have high or low risk to develop active TB is proposed to investigate the impact of new immigrants in early latent or late latent stage on TB incidence of foreign-born population in immigration countries using real TB data from Canada.

In Chapter 8, a TB model with partial immunity and relapses is proposed to investigate the effects of loss of immunity on basic reproduction number and TB incidence rate in a high TB incidence country. Simulations are carried out using real TB data from South Africa.

Part 1
A Graph-Theoretical Approach to the Method of Global Lyapunov Functions

Mathematical models for infectious diseases in heterogenous population typically consist of a large number of equations: an n-group SEIR model is a system of $3n$ nonlinear differential equations, where n is an integer. To establish the global stability of disease-free and endemic equilibria of such a system, the only feasible general method has been the method of global Lyapunov functions. In applying this method, one needs to determine the sign of the derivative of the Lyapunov function, which is the sum of a huge number of signed terms (of the order n^n). This turns out to be a very difficult task. In the literature of mathematical epidemiology, the global stability results for heterogenous models are few, and majority of the existing results are only partial results.

In this part, we present a new approach to the method of Lyapunov functions, particularly tailored for large scale systems. We show that how results from graph theory can be used to characterize the patterns of the terms in the derivative V' of the Lyapunov function. Such a pattern characterization leads to the most natural grouping of terms and the determination of the sign of V'. For many classes of epidemic models, this approach leads to complete resolution of the global stability of the endemic equilibrium. We choose to demonstrate our approach using two typical and very general classes heterogenous models: multi-group models (Chapter 2) and multi-stage models (Chapter 3).

Chapter 1. Results from Graph Theory

In this chapter, some materials from graph theory are presented, they will be the basis for our graph-theoretical approach for global stability of endemic equilibrium of general compartmental models for disease transmission. In Section 1.1, basic concepts of graphs and directed trees are given. Section 1.2 describes the relationship between square matrices and the associated directed graphs. In Section 1.3, we give an important result from graph theory that describes solutions of a linear algebraic system using directed rooted trees. In Section 1.4, we describe unicyclic graphs and their weights. We also show how unicyclic graphs can be constructed from directed rooted trees by adding a directed arc, and their relation to certain products that will occur in applications in later chapters.

Graph theory has a long history and has been a very powerful tool in applications to many different fields arising from science, engineering, even sociology. Recently, more and more methods originating from graph theory are applied to epidemiological and biological research fields. Keeling and Eames [81] reviewed the relationships between networks and epidemic models and some of the ideas of modeling infectious diseases come from graph theory directly. In [115], a graph-theoretical approach was used to find to patterns among many factors in genomic medicine. In modeling gene networks, combinatorial skills help to explore the structures in directed graphs on a n-hypercube [40]. Solimano and Beretta [124] used some basic graph ideas to derive global stability in predator-prey systems. B. L. Clarke used graph techniques to study the chemical reaction networks [30]. In [120], applications of graph theory and combinatorics to problems from biological and social sciences were presented. In [119], graph theory was used to simplify and analyze the control problems from industry. In [36], a graph-reduction method was used to compute net reproductive value for discrete matrix

models. The book of Chen [26] provided a comprehensive and easy-to-use techniques for analyzing electrical circuits using graph theory.

1.1 Basic definitions of graphs

Graph theory provides a useful tool to tackle complicated problems occurring in completely different fields. In this section the basic vocabulary of graph theory is outlined. The definitions and concepts introduced here are needed for the approach developed in this chapter. We refer the reader to [26, 110, 119] for more detailed studies of graph theory.

A *graph* is a mathematical structure which consists of two sets: *vertex-set*, the set of vertices (or nodes, points), and *edge-set*, the set of edges (or arcs) whose two endpoints are vertices. Often a graph is denoted by G, the vertex-set and the edge-set by $V = \{v_1, v_2, \cdots, v_n, \cdots\}$ and $E = \{e_1, e_2, \cdots, e_n, \cdots\}$, respectively. If both V and E are finite sets, then the graph is called a *finite graph*. In this thesis only finite graphs are considered. The following diagram is a graph with 4 vertices and 3 edges. The vertex-set is $V = \{S, E, I, R\}$ and edge-set is $E = \{e_1, e_2, e_3\}$, see Figure 1.1.

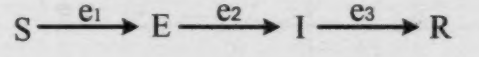


Figure 1.1: A finite graph with 4 vertices and 3 edges.

Any edge may be specified by the vertices that it connects. These vertices are called *end-vertices* of the edge under consideration. A *self-loop* is an edge whose end-vertices coincide. Any edge is said to be *incident* with its end-vertices and two vertices are *adjacent* if they are connected by an edge. The *degree* of a vertex is the number of edges incident with it. An end-vertex of a graph is a vertex of degree one.

By removing some edges and/or vertices of a given graph G, one obtains a *subgraph* G' of G, denoted by $G' \subset G$. The removal of a vertex implies the removal of every edge incident with it. The removal of edges, however, does not imply the removal of its end vertices.

For the purpose of practical application, it is necessary to consider the graph with orientation (*labeled graphs*). A graph whose every edge is equipped with a direction (or orientation) is called a *directed graph*, for short, *digraph*. Then each edge has an initial

vertex and final vertex. It is often useful to assign a number to each edge of a digraph and to call it *edge weight*. The weight of each edge can also be literal. In this thesis, only literal weight is used. Then a digraph augmented in this way is called a *weighted digraph*. A directed graph or digraph is illustrated in Figure 1.2.

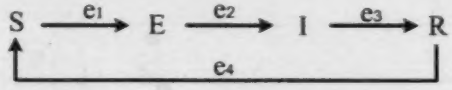


Figure 1.2: A digraph or directed graph.

Important classes of (sub-) digraph with special structures are paths, cycles and trees. A *directed path* is a sequence of edges $\{e_i, e_j, \cdots\}$ such that the initial vertex of the succeeding edge is the final vertex of the preceding edge. The number of edges contained in the sequence $\{e_i, e_j, \cdots\}$ is called the *length* of the path. A path is called *simple* if one reaches no vertex more than once, going along the path from its initial to its final vertex no vertex more than once. In Figure 1.2, the path $\{e_1, e_2, e_3\}$ is a directed path with length 3 and is a simple path.

A *closed path* is a path whose initial and final vertices are the same. A closed path is called a *cycle* if one reaches no vertex along the path, other than the initial-final vertex, more than once. The number of edges contained in a cycle defines the length of this cycle. Cycles of length 1 are called *self-cycles*. Figure 1.3 contains a self-cycle $\{e_1\}$ and closed path $\{e_2, e_3, e_4, e_5\}$ with length 4, see Figure 1.3.

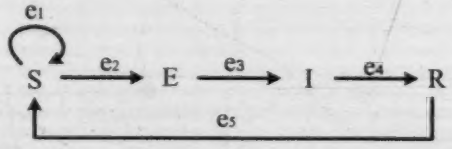


Figure 1.3: A digraph with a self-loop and a closed path.

A *tree* is a connected graph that has no cycles. A tree with n vertices is usually denoted as T_n. A *spanning tree* (complete tree) of a connected graph G is a subgraph which is a tree that involves all the vertices of G. A digraph is said to have a *root* r if r is a vertex and, for every other vertex v, there is a path which starts in r and ends in v. A digraph G is called a *rooted tree* if G has a root from which there is a unique path to every other vertex. The following figure 1.4 is a list of trees with up to 6 vertices.

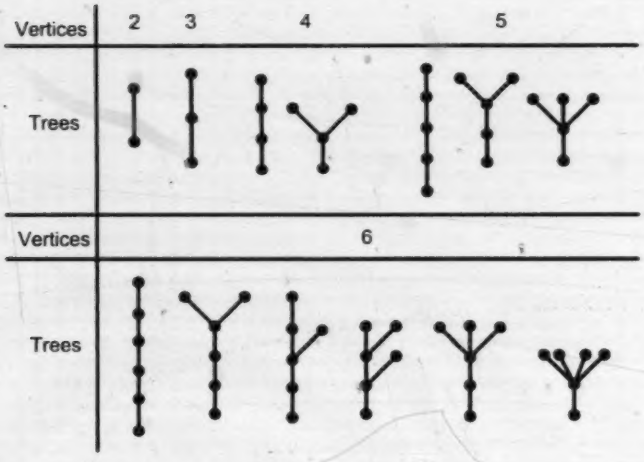


Figure 1.4: Table of trees with n vertices ($2 \leq n \leq 6$).

An important result of trees in graph theory is the Cayley formula (1889), which will be used later in this thesis. For its origin and proof, we refer the reader to [110].

Proposition 1.1. ***(Cayley formula):*** *Let $T(n)$ denote the total number of tree T_n with n labeled vertices, for any n, then*

$$T(n) = n^{n-2}. \tag{1.1}$$

A graph is *connected* if every pair of vertices is joined by a path. A digraph, is *strongly connected* if any two distinct vertices are joined by an oriented path between them.

1.2 Association between digraphs and square matrices

The analysis of a general linear system reduces ultimately to the solution of a simultaneous linear algebraic equations. *Directed-Graph Approach* is an alternative method to conventional algebraic methods of solving the system, by considering the properties of certain directed graphs associated with the system. The unknown variables of the equations correspond to the vertices of the graph, while the linear

relations between them appear in the form of directed edges connecting the vertices [26].

The basic idea of associating a directed graph with a linear algebraic system of linear equations was first introduced by MASON in 1953 and the graph is called a *signal-flow graph*. Later in 1959 COATES used *flow graph* to represent alternatively the equations as a directed graph. The idea of the correspondence between the terms in the expansion of a determinant of a matrix and the corresponding subgraphs in an associated directed graph $G(A)$ dates back to 1916. König first applied a graph-theoretic approach to the evaluations of a determinant. We refer the reader to [26, 119] for more comprehensive studies.

Let $A = (a_{ij})$ be a square matrix with order of n. The *directed graph $G(A)$ associated with A* is a digraph of n vertices, $1, 2, \cdots, n$, such that there exists an arc (j, k) leading from j to k if and only if $a_{kj} \neq 0$. For $i \neq j, a_{ij}$ is the weight of directed arc from vertex j to vertex i, and a_{ii} is the weight of the self-loop from vertex i to itself, see Figure 1.5.

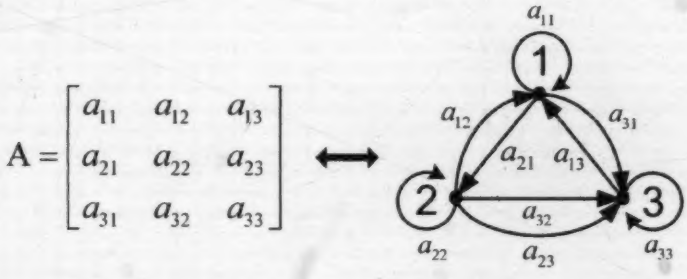


Figure 1.5: A square matrix A and its associated directed graph $G(A)$.

For $n > 1$, an $n \times n$ matrix A is *reducible* if, for some permutation matrix P,

$$PAP^T = \begin{bmatrix} A_1 & 0 \\ A_2 & A_3 \end{bmatrix},$$

and A_1, A_3 are square matrices. Otherwise, A is *irreducible*. Irreducibility has relationship with strongly connected digraphs. Then the following proposition is important and useful.

Proposition 1.2. *Square matrix A is irreducible if and only if $G(A)$ is strongly connected.*

For proof, we refer the reader to [10]. In Figure 1.6, two examples are given to illustrate Proposition 1.2.

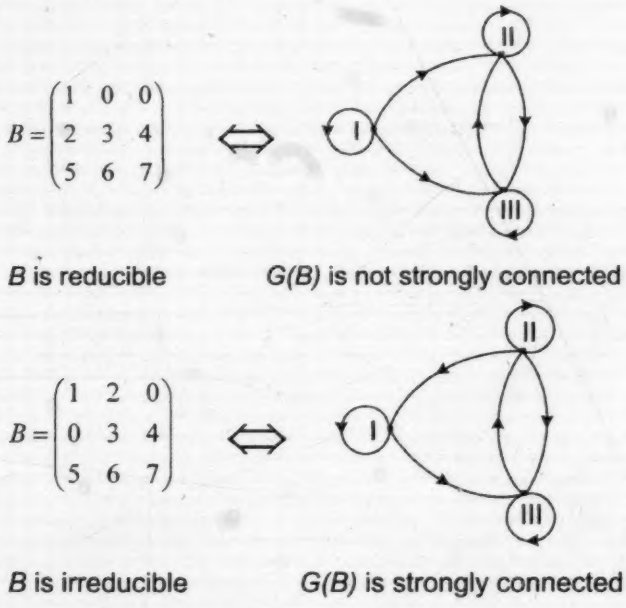


Figure 1.6: Examples of reducible and irreducible matrices and their associated directed graphs.

1.3 Directed rooted trees and solutions to linear algebraic systems

Consider a linear algebraic system

$$\overline{B}v = 0, \tag{1.2}$$

where

$$\overline{B} = \begin{bmatrix} \sum_{l\neq 1}\bar{\beta}_{1l} & -\bar{\beta}_{21} & \cdots & -\bar{\beta}_{n1} \\ -\bar{\beta}_{12} & \sum_{l\neq 2}\bar{\beta}_{2l} & \cdots & -\bar{\beta}_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ -\bar{\beta}_{1n} & -\bar{\beta}_{2n} & \cdots & \sum_{l\neq n}\bar{\beta}_{nl} \end{bmatrix}, \tag{1.3}$$

with $\bar{\beta}_{ij} \geq 0$, and $v = (v_1, \cdots, v_n)^T$ is a column vector. We have the following proposition.

Proposition 1.3. *Assume that the matrix $(\bar{\beta}_{ij})_{n\times n}$ is irreducible and $n \geq 2$. Then the followings hold.*

(1) *The solution space of system* (1.2) *has dimension 1.*

(2) *A basis of the solution space is given by*

$$(v_1, v_2, \ldots, v_n) = (C_{11}, C_{22}, \ldots, C_{nn}), \tag{1.4}$$

where C_{kk} denotes the cofactor of the k-th diagonal entry of $\overline{B}$, $1 \leq k \leq n$.

(3) *For all $1 \leq k \leq n$,*

$$C_{kk} = \sum_{T\in\mathbb{T}_k} \prod_{(j,h)\in E(T)} \bar{\beta}_{jh}, \tag{1.5}$$

where $\mathbb{T}_k$ is the set of all directed n-trees rooted at the k-th vertex, and $E(T)$ denotes the set of arcs in a directed tree T.

(4) *For all $1 \leq k \leq n$,*

$$C_{kk} > 0.$$

Proof. Since the sum of each column in $\overline{B}$ equals zero, we have

$$C_{jk} = C_{lk}, \quad 1 \leq j, k, l \leq n, \tag{1.6}$$

where C_{jk} denotes the cofactor of the (j, k) entry of $\overline{B}$. Since $\overline{B}$ is singular, we know that $(C_{11}, C_{12}, \ldots, C_{1n})$ is a solution of system (1.2). Therefore, by (1.6), $(C_{11}, C_{22}, \ldots, C_{nn})$ is also a solution of system (1.2).

For $1 \leq k \leq n$, in the k-th column of $\overline{B}$, the diagonal entry, $\sum_{l\neq k} \bar{\beta}_{kl}$, equals the negative of the sum of nondiagonal entries. By a result on directed graphs in [110, p. 47, Theorem 5.5], we obtain

$$C_{kk} = \sum_{T\in\mathbb{T}_k} \prod_{(j,h)\in E(T)} \bar{\beta}_{jh}.$$

Since $(\bar{\beta}_{ij})$ is irreducible, its associated directed graph is strongly connected, by Proposition 1.2. Thus, for each k, at least one term in $\sum_{T\in\mathbb{T}_k}\prod_{(j,h)\in E(T)}\bar{\beta}_{jh}$ is positive. Therefore, $C_{kk} > 0$ for $k = 1, 2, \ldots, n$. Since C_{11} is a $n-1$ minor of $\overline{B}$, we know $\text{rank}(\overline{B}) = n-1$, and the solution space of (1.2) has dimension 1, completing the proof of Proposition 1.3. ∎

We give an illustration of (1.5), for the case $n = 3$. Then (1.2) becomes

$$\begin{bmatrix} \bar{\beta}_{12}+\bar{\beta}_{13} & -\bar{\beta}_{21} & -\bar{\beta}_{31} \\ -\bar{\beta}_{12} & \bar{\beta}_{21}+\bar{\beta}_{23} & -\bar{\beta}_{32} \\ -\bar{\beta}_{13} & -\bar{\beta}_{23} & \bar{\beta}_{31}+\bar{\beta}_{32} \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}. \tag{1.7}$$

By (1.4), we have

$$v_1 = C_{11} = \begin{vmatrix} \bar{\beta}_{21}+\bar{\beta}_{23} & -\bar{\beta}_{32} \\ -\bar{\beta}_{23} & \bar{\beta}_{31}+\bar{\beta}_{32} \end{vmatrix} = \bar{\beta}_{32}\bar{\beta}_{21}+\bar{\beta}_{31}\bar{\beta}_{21}+\bar{\beta}_{23}\bar{\beta}_{31},$$

$$v_2 = C_{22} = \begin{vmatrix} \bar{\beta}_{12}+\bar{\beta}_{13} & -\bar{\beta}_{31} \\ -\bar{\beta}_{13} & \bar{\beta}_{31}+\bar{\beta}_{32} \end{vmatrix} = \bar{\beta}_{12}\bar{\beta}_{31}+\bar{\beta}_{12}\bar{\beta}_{32}+\bar{\beta}_{13}\bar{\beta}_{32},$$

$$v_3 = C_{33} = \begin{vmatrix} \bar{\beta}_{12}+\bar{\beta}_{13} & -\bar{\beta}_{21} \\ -\bar{\beta}_{12} & \bar{\beta}_{21}+\bar{\beta}_{23} \end{vmatrix} = \bar{\beta}_{12}\bar{\beta}_{23}+\bar{\beta}_{13}\bar{\beta}_{21}+\bar{\beta}_{13}\bar{\beta}_{23}.$$

Let $\mathbb{T}_k$ be the set of all directed trees rooted at the vertex k in the directed graph associated with matrix $\overline{B}$, $k = 1, 2, 3$, see Figure 1.7. Then, $\mathbb{T}_1 = \{T_1^1, T_1^2, T_1^3\}$, $\mathbb{T}_2 = \{T_2^1, T_2^2, T_2^3\}$, $\mathbb{T}_3 = \{T_3^1, T_3^2, T_3^3\}$, and

$$E(T_1^1) = \{(3,2),(2,1)\},\ E(T_1^2) = \{(2,1),(3,1)\},\ E(T_1^3) = \{(2,3),(3,1)\}.$$

$$E(T_2^1) = \{(3,1),(1,2)\},\ E(T_2^2) = \{(3,2),(1,2)\},\ E(T_2^3) = \{(1,3),(3,2)\}.$$

$$E(T_3^1) = \{(2,1),(1,3)\},\ E(T_3^2) = \{(1,2),(2,3)\},\ E(T_3^3) = \{(1,3),(2,3)\}.$$

Therefore,

$$\sum_{T_1^i\in\mathbb{T}_1}\prod_{(j,h)\in E(T_1^i)}\bar{\beta}_{jh} = \bar{\beta}_{32}\bar{\beta}_{21}+\bar{\beta}_{21}\bar{\beta}_{31}+\bar{\beta}_{23}\bar{\beta}_{31} = C_{11}, \tag{1.8}$$

$$\sum_{T_2^i\in\mathbb{T}_2}\prod_{(j,h)\in E(T_2^i)}\bar{\beta}_{jh} = \bar{\beta}_{31}\bar{\beta}_{12}+\bar{\beta}_{32}\bar{\beta}_{12}+\bar{\beta}_{13}\bar{\beta}_{32} = C_{22}, \tag{1.9}$$

$$\sum_{T_3^i\in\mathbb{T}_3}\prod_{(j,h)\in E(T_3^i)}\bar{\beta}_{jh} = \bar{\beta}_{21}\bar{\beta}_{13}+\bar{\beta}_{12}\bar{\beta}_{23}+\bar{\beta}_{13}\bar{\beta}_{23} = C_{33}. \tag{1.10}$$

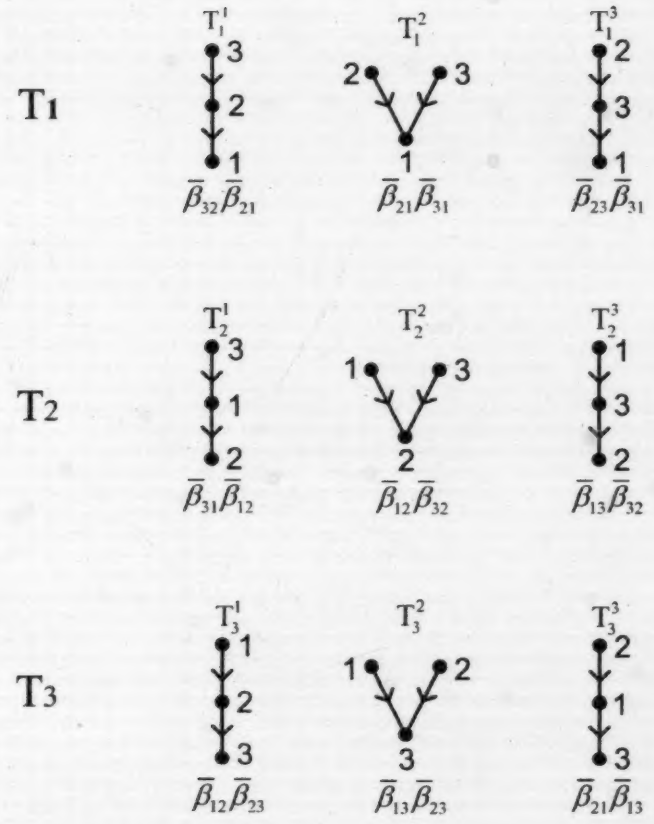


Figure 1.7: All directed rooted 3-trees and their weights.

1.4 Unicyclic digraphs and their weights

Let

$$v_k = \sum_{T \in \mathbb{T}_k} \prod_{(j,h) \in E(T)} \bar{\beta}_{jh}, \quad k = 1, \cdots, n,$$

be the solution basis to system (1.2). We know that

$$\prod_{(j,h) \in E(T)} \bar{\beta}_{jh}$$

can be regarded as the weight of a directed tree T rooted at vertex k. In our application of Lyapunov function in later chapters, we will be dealing with products of form

$$v_k \bar{\beta}_{kj}, \quad k, j = 1, \cdots, n,$$

which are sum of products of n $\bar{\beta}_{pq}$'s. Each of these products is the weight of a unicyclic n-digraph, formed from the directed tree $T \in \mathbb{T}_k$ by adding a directed edge from the root k to vertex j. In Figures 1.8 – 1.10, we have illustrated all the products in $v_k \bar{\beta}_{kj}$, and their unicyclic graphs for the case $n = 3$.

A closer examination of Figures 1.8 – 1.10 reveals that not all the unicyclic graphs are distinct. For instance, the unicyclic graphs $\{(2,3),(3,1),(1,3)\}$ appears twice in different configurations, see Figure 1.11. The two corresponding weights, though written in different orders since $\bar{\beta}_{23}\bar{\beta}_{31}\bar{\beta}_{13}$ appears in $v_1\bar{\beta}_{13}$ and $\bar{\beta}_{13}\bar{\beta}_{23}\bar{\beta}_{31}$ appears in $v_3\bar{\beta}_{31}$, are equal.

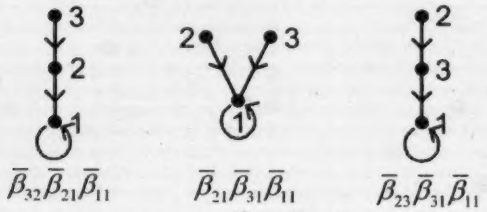
Similarly, the unicyclic graph $\{(1,2),(2,3),(3,1)\}$ appears three times in three different configurations, see Figure 1.12. The three corresponding weights, appearing in $v_1\bar{\beta}_{12}$, $v_2\bar{\beta}_{23}$ and $v_3\bar{\beta}_{31}$, respectively, are all equal.

The following patterns can be summarized:

1. Products in Figure 1.8 - 1.10 that correspond to the same unicyclic graph are all equal.

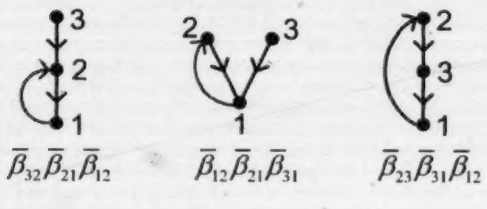
2. The number of products in Figure 1.8 - 1.10 that correspond to the same unicyclic graph Q is equal to the length of the cycle in Q. For instance, the unicyclic graph $\{(2,3),(3,1),(1,3)\}$ in Figure 1.11 has a 2-cycle, and the unicyclic graph $\{(1,2),(2,3),(3,1)\}$ in Figure 1.12 has a 3-cycle.

$$v_1\overline{\beta}_{11} = \overline{\beta}_{32}\overline{\beta}_{21}\overline{\beta}_{11} + \overline{\beta}_{21}\overline{\beta}_{31}\overline{\beta}_{11} + \overline{\beta}_{23}\overline{\beta}_{31}\overline{\beta}_{11}$$



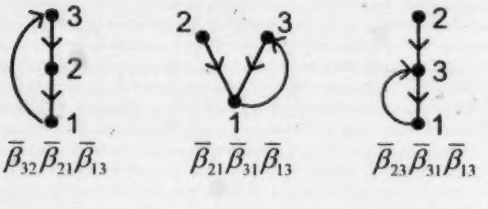
$\overline{\beta}_{32}\overline{\beta}_{21}\overline{\beta}_{11}$ $\quad$ $\overline{\beta}_{21}\overline{\beta}_{31}\overline{\beta}_{11}$ $\quad$ $\overline{\beta}_{23}\overline{\beta}_{31}\overline{\beta}_{11}$

$$v_1\overline{\beta}_{12} = \overline{\beta}_{32}\overline{\beta}_{21}\overline{\beta}_{12} + \overline{\beta}_{21}\overline{\beta}_{31}\overline{\beta}_{12} + \overline{\beta}_{23}\overline{\beta}_{31}\overline{\beta}_{12}$$



$\overline{\beta}_{32}\overline{\beta}_{21}\overline{\beta}_{12}$ $\quad$ $\overline{\beta}_{12}\overline{\beta}_{21}\overline{\beta}_{31}$ $\quad$ $\overline{\beta}_{23}\overline{\beta}_{31}\overline{\beta}_{12}$

$$v_1\overline{\beta}_{13} = \overline{\beta}_{32}\overline{\beta}_{21}\overline{\beta}_{13} + \overline{\beta}_{21}\overline{\beta}_{31}\overline{\beta}_{13} + \overline{\beta}_{23}\overline{\beta}_{31}\overline{\beta}_{13}$$



$\overline{\beta}_{32}\overline{\beta}_{21}\overline{\beta}_{13}$ $\quad$ $\overline{\beta}_{21}\overline{\beta}_{31}\overline{\beta}_{13}$ $\quad$ $\overline{\beta}_{23}\overline{\beta}_{31}\overline{\beta}_{13}$

Figure 1.8: Unicyclic graphs representing products in $v_1\beta_{1j}, j = 1, 2, 3$.

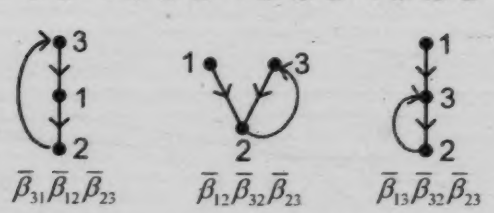
$$v_2\bar{\beta}_{21} = \bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{21} + \bar{\beta}_{12}\bar{\beta}_{32}\bar{\beta}_{21} + \bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{21}$$

$\bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{21}$ $\bar{\beta}_{12}\bar{\beta}_{32}\bar{\beta}_{21}$ $\bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{21}$

$$v_2\bar{\beta}_{22} = \bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{22} + \bar{\beta}_{12}\bar{\beta}_{32}\bar{\beta}_{22} + \bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{22}$$

$\bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{22}$ $\bar{\beta}_{12}\bar{\beta}_{32}\bar{\beta}_{22}$ $\bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{22}$

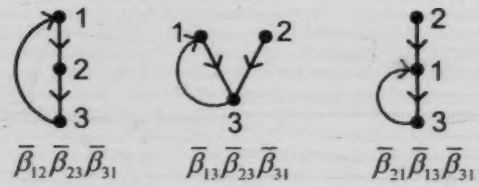
$$v_2\bar{\beta}_{23} = \bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{23} + \bar{\beta}_{12}\bar{\beta}_{32}\bar{\beta}_{23} + \bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{23}$$



$\bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{23}$ $\bar{\beta}_{12}\bar{\beta}_{32}\bar{\beta}_{23}$ $\bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{23}$

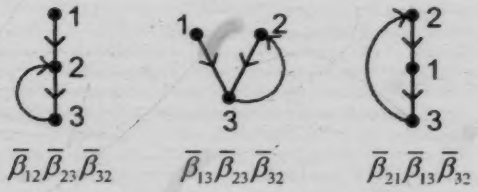
Figure 1.9: Unicyclic graphs representing products in $v_2\beta_{2j}, j = 1, 2, 3$.

$$v_3\overline{\beta}_{31} = \overline{\beta}_{12}\overline{\beta}_{23}\overline{\beta}_{31} + \overline{\beta}_{13}\overline{\beta}_{23}\overline{\beta}_{31} + \overline{\beta}_{21}\overline{\beta}_{13}\overline{\beta}_{31}$$



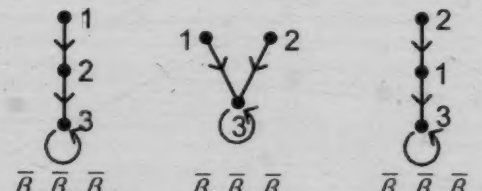
$\overline{\beta}_{12}\overline{\beta}_{23}\overline{\beta}_{31}$ $\overline{\beta}_{13}\overline{\beta}_{23}\overline{\beta}_{31}$ $\overline{\beta}_{21}\overline{\beta}_{13}\overline{\beta}_{31}$

$$v_3\overline{\beta}_{32} = \overline{\beta}_{12}\overline{\beta}_{23}\overline{\beta}_{32} + \overline{\beta}_{13}\overline{\beta}_{23}\overline{\beta}_{32} + \overline{\beta}_{21}\overline{\beta}_{13}\overline{\beta}_{32}$$



$\overline{\beta}_{12}\overline{\beta}_{23}\overline{\beta}_{32}$ $\overline{\beta}_{13}\overline{\beta}_{23}\overline{\beta}_{32}$ $\overline{\beta}_{21}\overline{\beta}_{13}\overline{\beta}_{32}$

$$v_3\overline{\beta}_{33} = \overline{\beta}_{12}\overline{\beta}_{23}\overline{\beta}_{33} + \overline{\beta}_{13}\overline{\beta}_{23}\overline{\beta}_{33} + \overline{\beta}_{21}\overline{\beta}_{13}\overline{\beta}_{33}$$



$\overline{\beta}_{12}\overline{\beta}_{23}\overline{\beta}_{33}$ $\overline{\beta}_{13}\overline{\beta}_{23}\overline{\beta}_{33}$ $\overline{\beta}_{21}\overline{\beta}_{13}\overline{\beta}_{33}$

Figure 1.10: Unicyclic graphs representing products in $v_3\beta_{3j}, j = 1, 2, 3$.

$\overline{\beta}_{23}\overline{\beta}_{31}\overline{\beta}_{13}$ $\overline{\beta}_{13}\overline{\beta}_{23}\overline{\beta}_{31}$

Figure 1.11: Two configurations of a unicyclic graph with a 2-cycle.

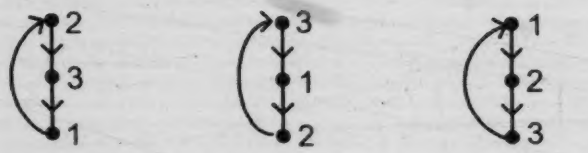


Figure 1.12: Three configurations of a unicyclic graph with a 3-cycle.

3. The total number of products in Figure 1.8 - 1.10 is 3^3. The number of distinct products can be counted using distinct unicyclic graphs. Let $D(3,r)$ be the number of unicyclic 3-graphs with a r-cycle, $r = 1,2,3$. Then

$$D(3,1) = 9, \quad D(3,2) = 6, \quad D(3,3) = 2.$$

The relation between $D(3,r)$ and the number of all the products is

$$D(3,1)\cdot 1 + D(3,2)\cdot 2 + D(3,3)\cdot 3 = 3^3.$$

4. In general, for $k,j = 1,\cdots,n$, there are n^n products in all expression of $v_k\bar{\beta}_{kj}$, each represented as the weight of a unicyclic n-digraph. The products represented by the same unicyclic graph are the same. A unicyclic graph with a r-cycle represents r products.

5. Let $D(n,r)$ be the number of unicyclic n-digraph with a r-cycle, $1 \le r \le n$. Then the following relations are well-known in graph theory (see e.g. [9, Chapter 2]).

$$D(n,r) = \binom{n}{r} n^{n-r-1}\, r!, \tag{1.11}$$

$$n^n = \sum_{l=1}^{n} D(n,r)\, r. \tag{1.12}$$

Patterns summarized here and relations (1.11) and (1.12) will be extremely useful in Chapter 2 and Chapter 3, for the proof of the global stability of the endemic equilibrium, using the method of global Lyapunov functions. They allow us to group terms in the derivative of the Lyapunov function by unicyclic graphs.

Chapter 2. Global Dynamics of a Class of Multi-Group SEIR Models

Multi-group models have been proposed in the literature to describe the transmission dynamics of infectious diseases in heterogeneous host populations. Heterogeneity in host population can be the result of many factors. Individual hosts can be divided into groups according to different contact patterns such as those among children and adults for Measles and Mumps, or as distinct number of sexual partners for sexually transmitted diseases and HIV/AIDS. Groups can be geographical such as communities, cities, and countries, or epidemiological, to incorporate differential infectivity or co-infection of multiple strains of the disease agent. Multi-group models can also be used to investigate infectious diseases with multiple hosts such as West-Nile virus and vector borne diseases such as Malaria. For a recent survey of multi-group models, we refer the reader to [131].

In this chapter, the global dynamics for a class of multi-group SEIR models with varying group sizes are completely determined by the basic reproduction number R_0. In particular, we prove that when $R_0 \leq 1$, the disease-free equilibrium is globally stable in the feasible region. When $R_0 > 1$, the unique endemic equilibrium is globally asymptotically stable in the interior of feasible region. The uniqueness and global stability of the endemic equilibrium of the n-group SEIR models have been a well-known open problem in mathematical epidemiology. We completely resolve this open problem using the graph-theoretical approach proposed in Chapter 1. The whole procedure of the proof of global stability of endemic equilibrium illustrates our graph-theoretical approach in detail.

In Section 2.1, we formulate the multi-group SEIR model and recall the history of multi-group models. The basic reproduction number is calculated and compared with those in the literature in Section 2.2. The detailed proof of the main theorem in this

chapter is shown in Section 2.3 (Theorem 2.3).

2.1 Modeling infectious diseases in heterogenous populations

A multi-group (n-group, $n \geq 2$) model is, in general, formulated by dividing the population of size $N(t)$ into n distinct groups. For $1 \leq k \leq n$, the k-th group is further partitioned into four compartments: the susceptible, infected but not infectious (latent or exposed), infectious, and recovered, whose numbers of individuals at time t are denoted by $S_k(t), E_k(t), I_k(t)$, and $R_k(t)$, respectively. For $1 \leq k, j \leq n$, the disease transmission coefficient between compartments S_k and I_j is denoted by β_{kj}, so that the new infection occurred in the k-th group is given by

$$\sum_{j=1}^{n} \beta_{kj} S_k I_j. \tag{2.1}$$

The form of incidence in (2.1) is bilinear. Other incidence forms have been used in the literature, depending on the assumptions made about the mixing among different groups. The matrix $B = (\beta_{kj})_{n\times n}$ is the contact matrix, where $\beta_{kj} \geq 0$. Within the k-th group, it is assumed that natural death occurs in S_k, E_k, I_k, and R_k compartments with rate constants d_k^S, d_k^E, d_k^I, and d_k^R, respectively. Individuals in E_k becomes infectious with rate constant ϵ_k. The influx of individuals into the k-th group is given by a constant Λ_k. We assume that individuals in I_k suffer an additional death due to disease with rate constant θ_k and recover with a rate constant γ_k, once recovered they remain permanently immuned for the disease . Based on these assumptions, a n-group epidemic models of SEIR type with bilinear incidence, is described by the following system of differential equations

$$\begin{cases} S_k' = \Lambda_k - d_k^S S_k - \sum_{j=1}^{n} \beta_{kj} S_k I_j, \\ E_k' = \sum_{j=1}^{n} \beta_{kj} S_k I_j - (d_k^E + \epsilon_k) E_k, \quad k = 1, 2, \cdots, n. \\ I_k' = \epsilon_k E_k - (d_k^I + \gamma_k + \theta_k) I_k, \\ R_k' = \gamma_k I_k - d_k^R R_k. \end{cases} \tag{2.2}$$

The parameters in the model are summarized in the following list:

β_{kj}	:	transmission coefficient between compartments S_k and I_j.
$d_k^S, d_k^E, d_k^I, d_k^R$	:	natural death rates of S, E, I, R compartments in the k-th
	:	group, respectively.
Λ_k	:	influx of individuals into the k-th group.
ϵ_k	:	rate of becoming infectious after latent period.
γ_k	:	recovery rate of infectious individuals in the k-th group.
θ_k	:	disease-caused death rate in the k-th group.

All parameter values are assumed to be nonnegative and $d_k^S, d_k^E, d_k^I, d_k^R, \Lambda_k > 0$ for all k. We also assume that $\epsilon_k > 0$ and $d_k^* > 0$ where $d_k^* = \min\{d_k^S, d_k^E, d_k^I + \theta_k\}$. For other detailed discussions of the model and interpretations of parameters, we refer the reader to [131].

Observe that the variable R_k does not appear in the first three equations of (2.2). This allows us to consider first the following reduced system for S_k, E_k and I_k

$$\begin{cases} S_k' = \Lambda_k - d_k^S S_k - \sum_{j=1}^{n} \beta_{kj} S_k I_j, \\ E_k' = \sum_{j=1}^{n} \beta_{kj} S_k I_j - (d_k^E + \epsilon_k) E_k, \qquad k = 1, 2, \cdots, n. \\ I_k' = \epsilon_k E_k - (d_k^I + \gamma_k + \theta_k) I_k. \end{cases} \tag{2.3}$$

For each k, adding the three equations in (2.2) gives

$$\begin{aligned} (S_k + E_k + I_k)' &= \Lambda_k - d_k^S S_k - d_k^E E_k - (d_k^I + \theta_k) I_k \\ &\leq \Lambda_k - d_k^*(S_k + E_k + I_k), \end{aligned}$$

where d^* is defined as above. Hence $\limsup_{t\to\infty}(S_k + E_k + I_k) \leq \Lambda_k/d_k^*$. Similarly, from the S_k equation we obtain $\limsup_{t\to\infty} S_k \leq \Lambda_k/d_k^S$. Therefore, omega limit sets of system (2.3) are contained in the following bounded region in the non-negative cone of $\mathbb{R}^{3n}$

$$\Gamma = \left\{(S_1, E_1, I_1, \cdots, S_n, E_n, I_n) \in \mathbb{R}_+^{3n} \,|\, S_k \leq \frac{\Lambda_k}{d_k^S},\ S_k + E_k + I_k \leq \frac{\Lambda_k}{d_k^*},\ 1 \leq k \leq n\right\}. \tag{2.4}$$

Behaviors of R_k can then be determined from the last equation in (2.3). It can be verified that region Γ is positively invariant.

System (2.3) always has the disease-free equilibrium $P_0 = (S_1^0, 0, 0, \cdots, S_n^0, 0, 0)$ on the boundary of Γ, where $S_k^0 = \Lambda_k/d_k^S, k = 1, \cdots, n$. An equilibrium $P^* = (S_1^*, E_1^*, I_1^*, \cdots, S_n^*, E_n^*, I_n^*)$ in the interior $\overset{\circ}{\Gamma}$, of Γ, namely, $S_k^*, E_k^*, I_k^* > 0$, $1 \leq k \leq n$, is called an *endemic equilibrium*. The parameter $\beta_{kj} \geq 0$ is the transmission coefficient between compartments S_k and I_j, and $\beta_{kj} = 0$ if there is no transmission of the disease between the two compartments. The matrix $B = (\beta_{kj})$ encodes the patterns of contact and transmission among groups that are built into the model.

One of the earliest work on multigroup models is the seminal paper by Lajmanovich and Yorke [87] on a class of SIS multigroup models for the transmission dynamics of Gonorrhea. A complete analysis of the global dynamics is established. The global stability of the unique endemic equilibrium is proved using a quadratic global Lyapunov function. Global stability results also exist for other types of multi-group models, see e.g., [8, 67, 70, 99, 130]. Due to the large scale and complexity of multigroup models, progresses in the mathematical analysis of their global dynamics have been slow. In particular, the question of uniqueness and global stability of the endemic equilibrium, when the basic reproduction number R_0 is greater than 1, has largely been open. Hethcote [67] proved global stability of the endemic equilibrium for multigroup SIR model without vital dynamics. Beretta and Capasso [7] derived sufficient conditions for global stability of the endemic equilibrium for multigroup SIR model with constant population in each group. Thieme [130] proved global stability of the endemic equilibrium of multigroup SEIRS models under certain restrictions. The most recent result on global stability is given by Lin and So [99] for a class of SIRS models with constant group sizes, in which they proved that the endemic equilibrium is globally asymptotically stable if the cross-group contact rates are small or if the recovery rates in each group are small. The complete resolution of the global stability of endemic equilibrium when the basic reproduction number exceeds one has been a well-known open problem in mathematical epidemiology. On the other hand, results in the opposite direction also exist in the literature. For a class of n-group SIR models with proportional incidence, uniqueness of endemic equilibria may not hold when the basic reproduction number is greater than 1 (see [76, 131]). In light of these results, complete determination of the global dynamics of these models is essential for their application and further development. It is also crucial to determine how incidence forms or other epidemiological factors influence the uniqueness and global stability of

endemic equilibria (see [60]).

2.2 The basic reproduction number and preliminary analysis

Throughout this chapter, we assume that B is irreducible (see Section 1.2 for definition). Biologically, this is equivalent to assuming that any two groups S_i and I_j have a direct or indirect route of transmission. Let

$$R_0 = \rho(M_0), \tag{2.5}$$

denote the spectral radius of the matrix

$$M_0 = \left(\frac{\beta_{ij}\epsilon_i S_i^0}{(d_i^E + \epsilon_i)(d_i^I + \gamma_i + \theta_i)} \right)_{1 \le i,j \le n}.$$

The parameter R_0 is referred to as the basic reproduction number. In [59], we have derived our threshold parameter

$$R_0 = \rho \left(\begin{bmatrix} \frac{\beta_{11}\epsilon_1 S_1^0}{(d_1^E + \epsilon_1)(d_1^I + \gamma_1 + \theta_1)} & \cdots & \frac{\beta_{1n}\epsilon_1 S_1^0}{(d_1^E + \epsilon_1)(d_1^I + \gamma_1 + \theta_1)} \\ \vdots & \ddots & \vdots \\ \frac{\beta_{n1}\epsilon_n S_n^0}{(d_n^E + \epsilon_n)(d_n^I + \gamma_n + \theta_n)} & \cdots & \frac{\beta_{nn}\epsilon_n S_n^0}{(d_n^E + \epsilon_n)(d_n^I + \gamma_n + \theta_n)} \end{bmatrix} \right) \tag{2.6}$$

from the stability analysis of the disease-free equilibrium P_0 using the method of Lyapunov functions. We have shown that R_0 plays the role expected of the basic reproduction number, namely, if $R_0 \le 1$ the disease always dies out, and if $R_0 > 1$ the disease persists. In [135], a method of deriving the basic reproduction number for epidemic models in heterogeneous populations is proposed. Apply the method of [135] to our model (2.3), we can derive the basic reproduction number as

$$R_0 = \rho \left(\begin{bmatrix} \frac{\beta_{11}\epsilon_1 S_1^0}{(d_1^E + \epsilon_1)(d_1^I + \gamma_1 + \theta_1)} & \cdots & \frac{\beta_{1n}\epsilon_1 S_1^0}{(d_n^E + \epsilon_n)(d_n^I + \gamma_n + \theta_n)} \\ \vdots & \ddots & \vdots \\ \frac{\beta_{n1}\epsilon_n S_n^0}{(d_1^E + \epsilon_1)(d_1^I + \gamma_1 + \theta_1)} & \cdots & \frac{\beta_{nn}\epsilon_n S_n^0}{(d_n^E + \epsilon_n)(d_n^I + \gamma_n + \theta_n)} \end{bmatrix} \right), \tag{2.7}$$

where the matrix $\left(\frac{\beta_{kj}\epsilon_j S_k^0}{(d_j^E + \epsilon_j)(d_j^I + \gamma_j + \theta_j)} \right)$ is called the next generation matrix in [37] (see Example 4.2 in [135]). Biological interpretation of R_0 in (2.7) as the basic reproduction

number is given in [37, 131, 135]. It is straightforward to verify that two expressions of R_0 in [redacted] and (2.7) are equivalent.

System (2.3) is said to be uniformly persistent in $\overset{\circ}{\Gamma}$ if there exists constant $c > 0$ such that

$$\liminf_{t\to\infty} S_k(t) > c, \ \liminf_{t\to\infty} E_k(t) > c, \text{ and } \liminf_{t\to\infty} I_k(t) > c,$$

where $k = 1, \cdots, n$, provided $(S_1(0), E_1(0), I_1(0), \cdots, S_n(0), E_n(0), I_n(0)) \in \overset{\circ}{\Gamma}$.

The following result for system (2.3) is known in the literature, at least for some special classes of system (2.3), and its proof is standard (see [70, 130, 135]).

Proposition 2.1. *Assume $B = (\beta_{ij})$ is irreducible. Then followings statements hold.*

(1) *If $R_0 \leq 1$, then P_0 is the unique equilibrium and it is globally stable in Γ.*

(2) *If $R_0 > 1$, then P_0 is unstable and system (2.3) is uniformly persistent in $\overset{\circ}{\Gamma}$.*

For the proof, we refer the reader to [59, section 4] for detail.

Uniform persistence of (2.3), together with uniform boundedness of solutions in $\overset{\circ}{\Gamma}$, implies the existence of an equilibrium of (2.3) in $\overset{\circ}{\Gamma}$ (see Theorem D.3 in [122] or Theorem 2.8.6 in [12]).

Corollary 2.2. *Assume $B = (\beta_{ij})$ is irreducible. If $R_0 > 1$, then (2.3) has at least one endemic equilibrium.*

2.3 Global asymptotical stability of the endemic equilibrium

A long-standing open question in mathematical epidemiology is that whether a multi-group model such as system (2.3) has a unique endemic equilibrium P^* when $R_0 > 1$, and if so, whether P^* is globally stable when it is unique [131].

Denote an endemic equilibrium by

$$P^* = (S_1^*, E_1^*, I_1^*, S_2^*, E_2^*, I_2^*, \ldots, S_n^*, E_n^*, I_n^*),$$

$S_k^* > 0, E_k^*$ and $I_k^* > 0$ for $k = 1, 2, \ldots, n$. The following main result on the uniqueness and global stability of P^* when $R_0 > 1$ is established. Choose

$$\bar{\beta}_{ij} = \beta_{ij} S_i^* I_j^*, \quad 1 \leq i, j \leq n, \quad n \geq 2, \tag{2.8}$$

then we get the $n \times n$ matrix $\overline{B}$ as given in (1.3). If $B = (\beta_{ij})$ is assumed to be irreducible, then matrix (β_{ij}) is irreducible. Let $\{v_1, \cdots, v_n\}$, $v_k > 0$, be a basis for system (1.2), $\overline{B}v = 0$, as described in Proposition 1.3. We have the following main result.

Theorem 2.3. *Under the assumption that $B = (\beta_{ij})$ is irreducible, if $R_0 > 1$, then there exists a unique endemic equilibrium P^*, and P^* is globally asymptotically stable in $\overset{\circ}{\Gamma}$.*

The proof of Theorem 2.3 is given in the Subsections 2.3.1 - 2.3.3.

2.3.1 Global Lyapunov function

Let P^* be any endemic equilibrium, whose existence is assured by Corollary 2.2. We will prove that P^* is globally asymptotically stable. The global stability of P^* also implies its uniqueness. The global stability of P^* is proved by considering a global Lyapunov function

$$V = \sum_{k=1}^{n} v_k \Big[(S_k - S_k^* \ln S_k) + (E_k - E_k^* \ln E_k) + \frac{d_k^E + \epsilon_k}{\epsilon_k} (I_k - I_k^* \ln I_k) \Big], \tag{2.9}$$

where v_k are chosen as that in Proposition 1.3. Differentiating V along solutions to (2.3) and using the equilibrium equations

$$\Lambda_k = d_k^S S_k^* + \sum_{j=1}^{n} \beta_{kj} S_k^* I_j^*, \tag{2.10}$$

$$(d_k^E + \epsilon_k) E_k^* = \sum_{j=1}^{n} \beta_{kj} S_k^* I_j^*, \qquad \epsilon_k E_k^* = (d_k^I + \gamma_k + \theta_k) I_k^*, \tag{2.11}$$

and

$$\frac{(d_k^E + \epsilon_k)(d_k^I + \gamma_k + \theta_k)}{\epsilon_k} I_k^* = \sum_{j=1}^{n} \beta_{kj} S_k^* I_j^*, \tag{2.12}$$

which follows the last of (2.11), we obtain

$$\begin{aligned}
\dot{V} &= \sum_{k=1}^{n} v_k \Big[\Lambda_k - d_k^S S_k - \textstyle\sum_{j=1}^{n} \beta_{kj} S_k I_j - \Lambda_k \frac{S_k^*}{S_k} + d_k^S S_k^* + \sum_{j=1}^{n} \beta_{kj} S_k^* I_j \\
&\quad + \textstyle\sum_{j=1}^{n} \beta_{kj} S_k I_j - (d_k^E + \epsilon_k) E_k - \sum_{j=1}^{n} \beta_{kj} \frac{E_k^* S_k I_j}{E_k} + (d_k^E + \epsilon_k) E_k^* \\
&\quad + (d_k^E + \epsilon_k) E_k - \frac{(d_k^E + \epsilon_k)(d_k^I + \gamma_k + \theta_k)}{\epsilon_k} I_k - (d_k^E + \epsilon_k) \frac{I_k^* E_k}{I_k} \\
&\quad + \frac{(d_k^E + \epsilon_k)(d_k^I + \gamma_k + \theta_k)}{\epsilon_k} I_k^* \Big] \\
&= \sum_{k=1}^{n} v_k \Big[d_k^S S_k^* \Big(2 - \tfrac{S_k^*}{S_k} - \tfrac{S_k}{S_k^*} \Big) + \Big(\textstyle\sum_{j=1}^{n} \beta_{kj} S_k^* I_j - \frac{(d_k^E + \epsilon_k)(d_k^I + \gamma_k + \theta_k)}{\epsilon_k} I_k \Big) \\
&\quad + \Big(3 \textstyle\sum_{j=1}^{n} \beta_{kj} S_k^* I_j^* - \sum_{j=1}^{n} \beta_{kj} I_j^* \frac{(S_k^*)^2}{S_k} - \sum_{j=1}^{n} \beta_{kj} S_k I_j \frac{E_k^*}{E_k} - (d_k^E + \epsilon_k) E_k \frac{I_k^*}{I_k} \Big) \Big] \\
&\le \sum_{k=1}^{n} v_k \Big[\Big(\textstyle\sum_{j=1}^{n} \beta_{kj} S_k^* I_j - \frac{(d_k^E + \epsilon_k)(d_k^I + \gamma_k + \theta_k)}{\epsilon_k} I_k \Big) \\
&\quad + \Big(3 \textstyle\sum_{j=1}^{n} \beta_{kj} S_k^* I_j^* - \sum_{j=1}^{n} \beta_{kj} I_j^* \frac{(S_k^*)^2}{S_k} - \sum_{j=1}^{n} \beta_{kj} S_k I_j \frac{E_k^*}{E_k} - (d_k^E + \epsilon_k) E_k \frac{I_k^*}{I_k} \Big) \Big].
\end{aligned} \tag{2.13}$$

The inequality in (2.13) holds because $S_k^*/S_k + S_k/S_k^* \ge 2$, and the last equal sign holds if and only if $S_k = S_k^*$. In the above derivation, we have substituted the two incidences of Λ_k in $\dot{V}$ using (2.10). Next, we show

$$\sum_{k=1}^{n} v_k \Big[\sum_{j=1}^{n} \beta_{kj} S_k^* I_j - \frac{(d_k^E + \epsilon_k)(d_k^I + \gamma_k + \theta_k)}{\epsilon_k} I_k \Big] = 0 \tag{2.14}$$

for all $(I_1, \cdots, I_n) \in \mathbb{R}_+^n$. To see this, we note that

$$\sum_{k=1}^{n} v_k \sum_{j=1}^{n} \beta_{kj} S_k^* I_j = \sum_{j=1}^{n} v_j \sum_{k=1}^{n} \beta_{jk} S_j^* I_k = \sum_{k=1}^{n} \Big(\sum_{j=1}^{n} \beta_{jk} S_j^* v_j \Big) I_k. \tag{2.15}$$

It suffices to show

$$\sum_{j=1}^{n} \beta_{jk} S_j^* v_j = \frac{(d_k^E + \epsilon_k)(d_k^I + \gamma_k + \theta_k)}{\epsilon_k} v_k, \qquad k = 1, 2, \cdots, n. \tag{2.16}$$

In fact, from $\overline{B} v = 0$ in (1.2) and (2.8), using and (2.12), we have

$$\begin{bmatrix} \beta_{11} S_1^* I_1^* & \cdots & \beta_{n1} S_n^* I_1^* \\ \vdots & \ddots & \vdots \\ \beta_{1n} S_1^* I_n^* & \cdots & \beta_{nn} S_n^* I_n^* \end{bmatrix} \begin{bmatrix} v_1 \\ \vdots \\ v_n \end{bmatrix} = \begin{bmatrix} \sum_{j=1}^{n} \beta_{1j} S_1^* I_j^* v_1 \\ \vdots \\ \sum_{j=1}^{n} \beta_{nj} S_n^* I_j^* v_n \end{bmatrix} = \begin{bmatrix} \frac{(d_1^E + \epsilon_1)(d_1^I + \gamma_1)}{\epsilon_1} I_1^* v_1 \\ \vdots \\ \frac{(d_n^E + \epsilon_n)(d_n^I + \gamma_n)}{\epsilon_n} I_n^* v_n \end{bmatrix},$$

and this leads to (2.16). Using inequality (2.13) and identity (2.14) and $(d_k^E+\epsilon_k)E_k^* = \sum_{j=1}^n \beta_{kj}S_k^*I_j^*$, we have

$$\begin{aligned}
\dot{V} &\le \sum_{k=1}^n v_k\Big(3\sum_{j=1}^n \beta_{kj}S_k^*I_j^* - \sum_{j=1}^n \beta_{kj}S_k^*I_j^*\frac{S_k^*}{S_k} - \sum_{j=1}^n \beta_{kj}S_k^*I_j^*\frac{S_kI_j}{S_k^*I_j^*}\frac{E_k^*}{E_k} \\
&\quad -(d_k^E+\epsilon_k)E_k^*\frac{E_k}{E_k^*}\frac{I_k^*}{I_k}\Big) \\
&= \sum_{k=1}^n v_k\Big(3\sum_{j=1}^n \bar{\beta}_{kj} - \sum_{j=1}^n \bar{\beta}_{kj}\frac{S_k^*}{S_k} - \sum_{j=1}^n \bar{\beta}_{kj}\frac{S_kI_jE_k^*}{S_k^*I_j^*E_k} - \sum_{j=1}^n \bar{\beta}_{kj}\frac{E_k}{E_k^*}\frac{I_k^*}{I_k}\Big) \\
&= \sum_{k,j=1}^n v_k\bar{\beta}_{kj}\Big(3-\frac{S_k^*}{S_k} - \frac{S_kI_jE_k^*}{S_k^*I_j^*E_k} - \frac{E_kI_k^*}{E_k^*I_k}\Big).
\end{aligned} \tag{2.17}$$

Denote

$$\begin{aligned}
H_n &= H_n(S_1,E_1,I_1,\cdots,S_n,E_n,I_n) \\
&= \sum_{k,j=1}^n v_k\bar{\beta}_{kj}\Big(3-\frac{S_k^*}{S_k} - \frac{S_kI_jE_k^*}{S_k^*I_j^*E_k} - \frac{E_kI_k^*}{E_k^*I_k}\Big).
\end{aligned} \tag{2.18}$$

In the following, we show $H_n \le 0$ for all $(S_1,E_1,I_1,\cdots,S_n,E_n,I_n) \in \mathring{\Gamma}$. The key to our proof is a complete description of the patterns exhibited in the expressions of $v_k\bar{\beta}_{kj}$ as described in Sections 1.3 and 1.4.

2.3.2 Application of graph theory

To show $H_n \le 0$, we need to substitute the expression for v_k

$$v_k = \sum_{T\in\mathbf{T}_k}\prod_{(j,h)\in E(T)}\bar{\beta}_{jh}, \quad k=1,\cdots,n, \tag{2.19}$$

into (2.18), and expand the sums in

$$v_k\bar{\beta}_{kj}, \quad k,j=1,\cdots,n. \tag{2.20}$$

The expression

$$3-\frac{S_k^*}{S_k} - \frac{S_kI_jE_k^*}{S_k^*I_j^*E_k} - \frac{E_kI_k^*}{E_k^*I_k} \tag{2.21}$$

will be kept intact, since the subindices in the expression are the same as in the $\bar{\beta}_{kj}$ term of $v_k\bar{\beta}_{kj}$.

We first demonstrate the proof for the case $n=3$, and show how terms in H_3 are regrouped according to the unicyclic graphs representing each coefficient.

From (2.18), we know

$$
\begin{aligned}
H_3 &= \sum_{k,j=1}^{3} v_k\bar{\beta}_{kj}\Big(3-\frac{S_k^*}{S_k}-\frac{S_kI_jE_k^*}{S_k^*I_j^*E_k}-\frac{E_kI_k^*}{E_k^*I_k}\Big)\\
&= v_1\bar{\beta}_{11}\Big(3-\frac{S_1^*}{S_1}-\frac{S_1I_1E_1^*}{S_1^*I_1^*E_1}-\frac{E_1I_1^*}{E_1^*I_1}\Big)\\
&+ v_1\bar{\beta}_{12}\Big(3-\frac{S_1^*}{S_1}-\frac{S_1I_2E_1^*}{S_1^*I_2^*E_1}-\frac{E_1I_1^*}{E_1^*I_1}\Big)+v_1\bar{\beta}_{13}\Big(3-\frac{S_1^*}{S_1}-\frac{S_1I_3E_1^*}{S_1^*I_3^*E_1}-\frac{E_1I_1^*}{E_1^*I_1}\Big)\\
&+ v_2\bar{\beta}_{21}\Big(3-\frac{S_2^*}{S_2}-\frac{S_2I_1E_2^*}{S_2^*I_1^*E_2}-\frac{E_2I_2^*}{E_2^*I_2}\Big)\\
&+ v_2\bar{\beta}_{22}\Big(3-\frac{S_2^*}{S_2}-\frac{S_2I_2E_2^*}{S_2^*I_2^*E_2}-\frac{E_2I_2^*}{E_2^*I_2}\Big)\\
&+ v_2\bar{\beta}_{23}\Big(3-\frac{S_2^*}{S_2}-\frac{S_2I_3E_2^*}{S_2^*I_3^*E_2}-\frac{E_2I_2^*}{E_2^*I_2}\Big)\\
&+ v_3\bar{\beta}_{31}\Big(3-\frac{S_3^*}{S_3}-\frac{S_3I_1E_3^*}{S_3^*I_1^*E_3}-\frac{E_3I_3^*}{E_3^*I_3}\Big)+v_3\bar{\beta}_{32}\Big(3-\frac{S_3^*}{S_3}-\frac{S_3I_2E_3^*}{S_3^*I_2^*E_3}-\frac{E_3I_3^*}{E_3^*I_3}\Big)\\
&+ v_3\bar{\beta}_{33}\Big(3-\frac{S_3^*}{S_3}-\frac{S_3I_3E_3^*}{S_3^*I_3^*E_3}-\frac{E_3I_3^*}{E_3^*I_3}\Big),
\end{aligned}
\tag{2.22}
$$

where

$$
\begin{aligned}
v_1 &= \bar{\beta}_{32}\bar{\beta}_{21}+\bar{\beta}_{21}\bar{\beta}_{31}+\bar{\beta}_{23}\bar{\beta}_{31},\\
v_2 &= \bar{\beta}_{31}\bar{\beta}_{12}+\bar{\beta}_{32}\bar{\beta}_{12}+\bar{\beta}_{13}\bar{\beta}_{32},\\
v_3 &= \bar{\beta}_{21}\bar{\beta}_{13}+\bar{\beta}_{12}\bar{\beta}_{23}+\bar{\beta}_{13}\bar{\beta}_{23}.
\end{aligned}
\tag{2.23}
$$

Each product in v_k is the weight of a directed 3-tree, rooted at vertex k, $k=1,2,3$, as shown in Figure 1.7.

Expanding $v_k\bar{\beta}_{kj}$, $k,j=1,2,3$, we have

$$
\begin{aligned}
v_1\bar{\beta}_{11} &= \bar{\beta}_{32}\bar{\beta}_{21}\bar{\beta}_{11}+\bar{\beta}_{21}\bar{\beta}_{31}\bar{\beta}_{11}+\bar{\beta}_{23}\bar{\beta}_{31}\bar{\beta}_{11},\\
v_1\bar{\beta}_{12} &= \bar{\beta}_{32}\bar{\beta}_{21}\bar{\beta}_{12}+\bar{\beta}_{21}\bar{\beta}_{31}\bar{\beta}_{12}+\bar{\beta}_{23}\bar{\beta}_{31}\bar{\beta}_{12},\\
v_1\bar{\beta}_{13} &= \bar{\beta}_{32}\bar{\beta}_{21}\bar{\beta}_{13}+\bar{\beta}_{21}\bar{\beta}_{31}\bar{\beta}_{13}+\bar{\beta}_{23}\bar{\beta}_{31}\bar{\beta}_{13};\\
v_2\bar{\beta}_{21} &= \bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{21}+\bar{\beta}_{32}\bar{\beta}_{12}\bar{\beta}_{21}+\bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{21},\\
v_2\bar{\beta}_{22} &= \bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{22}+\bar{\beta}_{32}\bar{\beta}_{12}\bar{\beta}_{22}+\bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{22},\\
v_2\bar{\beta}_{23} &= \bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{23}+\bar{\beta}_{32}\bar{\beta}_{12}\bar{\beta}_{23}+\bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{23};\\
v_3\bar{\beta}_{31} &= \bar{\beta}_{21}\bar{\beta}_{13}\bar{\beta}_{31}+\bar{\beta}_{12}\bar{\beta}_{23}\bar{\beta}_{31}+\bar{\beta}_{13}\bar{\beta}_{23}\bar{\beta}_{31},\\
v_3\bar{\beta}_{32} &= \bar{\beta}_{21}\bar{\beta}_{13}\bar{\beta}_{32}+\bar{\beta}_{12}\bar{\beta}_{23}\bar{\beta}_{32}+\bar{\beta}_{13}\bar{\beta}_{23}\bar{\beta}_{32},\\
v_3\bar{\beta}_{33} &= \bar{\beta}_{21}\bar{\beta}_{13}\bar{\beta}_{33}+\bar{\beta}_{12}\bar{\beta}_{23}\bar{\beta}_{33}+\bar{\beta}_{13}\bar{\beta}_{23}\bar{\beta}_{33}.
\end{aligned}
\tag{2.24}
$$

As we have seen in Section 1.4, each product in $v_k\bar{\beta}_{kj}$ is the weight of a unicyclic graph, all of which are shown in Figures 1.8 - 1.10.

As we have described in Section 1.4, the 3^3 products in (2.24) can be divided into three groups, according to the unicyclic graphs representing them.

Group I: Unicyclic graphs with a 1-cycle, 9 in total as shown in Figure 2.1.

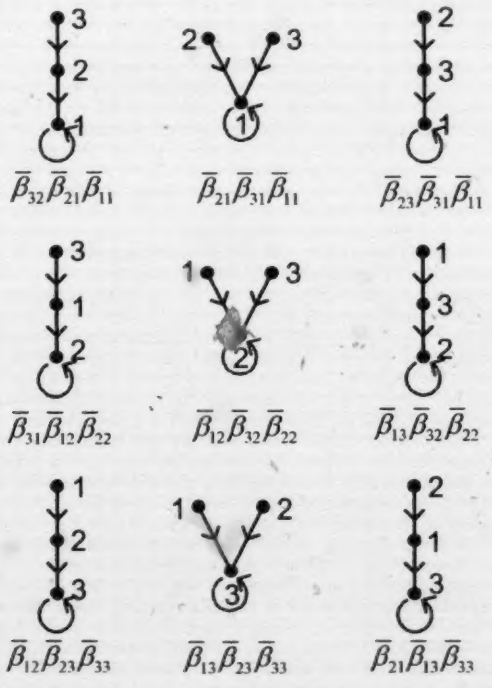


Figure 2.1: Unicyclic 3-digraphs with a 1-cycle and their weights.

Each unicyclic graph in Figure 2.1 represents one product in $v_1\bar{\beta}_{11}$, $v_2\bar{\beta}_{22}$, $v_3\bar{\beta}_{33}$ of (2.24).

Group II: Unicyclic graphs with a 2-cycle. There are 6 distinct unicyclic 2-digraphs with a 2-cycle, by (1.11). Each has two different configurations, leading to two different expressions of the same weight product, as we have pointed out in Section 1.4. This is again illustrated in Figure 2.2.

Group III: Unicyclic graphs with a 3-cycle. There are 2 distinct unicyclic 3-digraphs, each has three configurations, leading to three expressions of the same weight (product), see Figure 2.3.

According to the above grouping of products in (2.24), we can re-arrange the terms

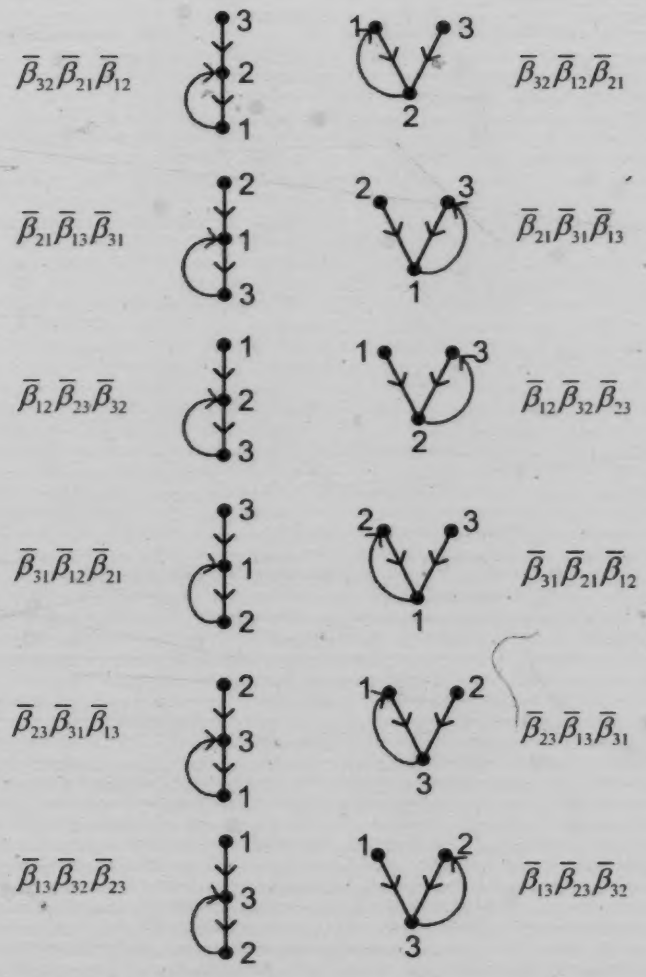


Figure 2.2: Each unicyclic 3-digraphs with a 2-cycle, has two configurations, producing two expressions of the same weight.

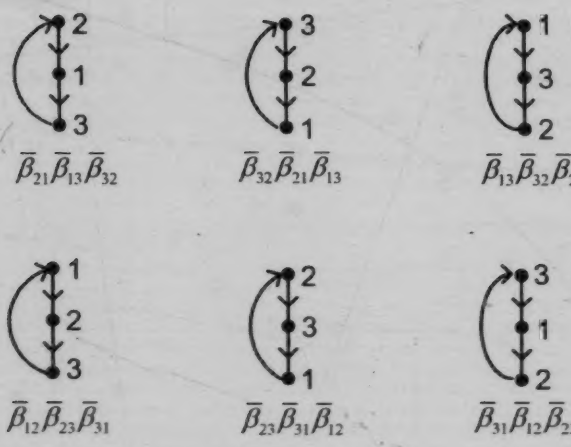


Figure 2.3: Each unicyclic 3-digraphs with a 3-cycle, has three configurations, producing three expressions of the same weight.

in H_3 as follows

$$
\begin{aligned}
H_3 = {} & \left(\bar{\beta}_{32}\bar{\beta}_{21}\bar{\beta}_{11} + \bar{\beta}_{21}\bar{\beta}_{31}\bar{\beta}_{11} + \bar{\beta}_{23}\bar{\beta}_{31}\bar{\beta}_{11}\right)\left[3 - \frac{S_1^*}{S_1} - \frac{S_1 I_1 E_1^*}{S_1^* I_1^* E_1} - \frac{E_1 I_1^*}{E_1^* I_1}\right] \\
& + \left(\bar{\beta}_{31}\bar{\beta}_{12}\bar{\beta}_{22} + \bar{\beta}_{32}\bar{\beta}_{12}\bar{\beta}_{22} + \bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{22}\right)\left[3 - \frac{S_2^*}{S_2} - \frac{S_2 I_2 E_2^*}{S_2^* I_2^* E_2} - \frac{E_2 I_2^*}{E_2^* I_2}\right] \\
& + \left(\bar{\beta}_{21}\bar{\beta}_{13}\bar{\beta}_{33} + \bar{\beta}_{12}\bar{\beta}_{23}\bar{\beta}_{33} + \bar{\beta}_{13}\bar{\beta}_{23}\bar{\beta}_{33}\right)\left[3 - \frac{S_3^*}{S_3} - \frac{S_3 I_3 E_3^*}{S_3^* I_3^* E_3} - \frac{E_3 I_3^*}{E_3^* I_3}\right] \\
& + \left(\bar{\beta}_{32}\bar{\beta}_{21}\bar{\beta}_{12} + \bar{\beta}_{12}\bar{\beta}_{21}\bar{\beta}_{31}\right)\left[6 - \frac{S_1^*}{S_1} - \frac{S_1 I_2 E_1^*}{S_1^* I_2^* E_1} - \frac{E_1 I_1^*}{E_1^* I_1} - \frac{S_2^*}{S_2} - \frac{S_2 I_1 E_2^*}{S_2^* I_1^* E_2} - \frac{E_2 I_2^*}{E_2^* I_2}\right] \\
& + \left(\bar{\beta}_{21}\bar{\beta}_{31}\bar{\beta}_{13} + \bar{\beta}_{23}\bar{\beta}_{31}\bar{\beta}_{13}\right)\left[6 - \frac{S_1^*}{S_1} - \frac{S_1 I_3 E_1^*}{S_1^* I_3^* E_1} - \frac{E_1 I_1^*}{E_1^* I_1} - \frac{S_3^*}{S_3} - \frac{S_3 I_1 E_3^*}{S_3^* I_1^* E_3} - \frac{E_3 I_3^*}{E_3^* I_3}\right] \\
& + \left(\bar{\beta}_{23}\bar{\beta}_{32}\bar{\beta}_{12} + \bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{23}\right)\left[6 - \frac{S_2^*}{S_2} - \frac{S_2 I_3 E_2^*}{S_2^* I_3^* E_2} - \frac{E_2 I_2^*}{E_2^* I_2} - \frac{S_3^*}{S_3} - \frac{S_3 I_2 E_3^*}{S_3^* I_2^* E_3} - \frac{E_3 I_3^*}{E_3^* I_3}\right] \\
& + \left(\bar{\beta}_{12}\bar{\beta}_{23}\bar{\beta}_{31}\right)\left[9 - \frac{S_1^*}{S_1} - \frac{S_1 I_2 E_1^*}{S_1^* I_2^* E_1} - \frac{E_1 I_1^*}{E_1^* I_1} - \frac{S_2^*}{S_2} - \frac{S_2 I_3 E_2^*}{S_2^* I_3^* E_2} - \frac{E_2 I_2^*}{E_2^* I_2}\right. \\
& \qquad \left. - \frac{S_3^*}{S_3} - \frac{S_3 I_1 E_3^*}{S_3^* I_1^* E_3} - \frac{E_3 I_3^*}{E_3^* I_3}\right] \\
& + \left(\bar{\beta}_{13}\bar{\beta}_{32}\bar{\beta}_{21}\right)\left[9 - \frac{S_1^*}{S_1} - \frac{S_1 I_3 E_1^*}{S_1^* I_3^* E_1} - \frac{E_1 I_1^*}{E_1^* I_1} - \frac{S_2^*}{S_2} - \frac{S_2 I_1 E_2^*}{S_2^* I_1^* E_2} - \frac{E_2 I_2^*}{E_2^* I_2}\right. \\
& \qquad \left. - \frac{S_3^*}{S_3} - \frac{S_3 I_2 E_3^*}{S_3^* I_2^* E_3} - \frac{E_3 I_3^*}{E_3^* I_3}\right]
\end{aligned}
\tag{2.25}
$$

It can be verified that expressions in each pair of parenthesis are non positive, by the

inequality

$$a_1 + a_2 + \cdots + a_n \geq n, \quad \text{if } a_i > 0 \text{ and } a_1 \cdot a_2 \cdot \cdots \cdot a_n = 1.$$

For instance, since

$$\frac{S_1^*}{S_1} \cdot \frac{S_1 I_2 E_1^*}{S_1^* I_2^* E_1} \cdot \frac{E_1 I_1^*}{E_1^* I_1} \cdot \frac{S_2^*}{S_2} \cdot \frac{S_2 I_1 E_2^*}{S_2^* I_1^* E_2} \cdot \frac{E_2 I_2^*}{E_2^* I_2} = 1,$$

we have

$$6 - \frac{S_1^*}{S_1} - \frac{S_1 I_2 E_1^*}{S_1^* I_2^* E_1} - \frac{E_1 I_1^*}{E_1^* I_1} - \frac{S_2^*}{S_2} - \frac{S_2 I_1 E_2^*}{S_2^* I_1^* E_2} - \frac{E_2 I_2^*}{E_2^* I_2} \leq 0.$$

We have thus shown

$$H_3 \leq 0,$$

for all nonnegative $(S_1, E_1, I_1, S_2, E_2, I_2, S_3, E_3, I_3)$.

For the general n, the same procedure as illustrated for $n = 3$ applies. We regroup the n^n products in $v_k \bar{\beta}_{kj}$, $k, j = 1, \cdots, n$, according to the cycle lengths of their corresponding unicyclic n-graphs.

For $1 \leq n$, let $\mathbb{D}(n, l)$ be the set of all unicyclic n-digraphs with a l-cycle. For each $Q \in \mathbb{D}(n, l)$ with the l-cycle $CQ = \{r_1, \cdots, r_l\}$ whose edge set is

$$E(CQ) = \{(r_1, r_2), (r_2, r_3), \cdots, (r_{l-1}, r_l), (r_l, r_1)\}.$$

We know that there are l products in the expansions of $v_k \bar{\beta}_{kj}$ that are all equal to the weight of Q, w_Q. Therefore, the l-terms in H_n with these l products as coefficients can be combined as

$$\begin{aligned} H_{n,Q} &= w_Q \sum_{(p,q) \in E(CQ)} \left(3 - \frac{S_p^*}{S_p} - \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} - \frac{E_p I_p^*}{E_p^* I_p}\right) \\ &= w_Q \left[3l - \sum_{(p,q) \in E(CQ)} \left(\frac{S_p^*}{S_p} + \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} + \frac{E_p I_p^*}{E_p^* I_p}\right)\right]. \end{aligned}$$

We can verify that

$$\prod_{(p,q) \in E(CQ)} \frac{S_p^*}{S_p} \cdot \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} \cdot \frac{E_p I_p^*}{E_p^* I_p} = \prod_{(p,q) \in E(CQ)} \frac{I_q I_p^*}{I_q^* I_p} = 1,$$

here CQ is a cycle. Therefore,

$$\sum_{(p,q) \in E(CQ)} \left(\frac{S_p^*}{S_p} + \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} + \frac{E_p I_p^*}{E_p^* I_p}\right) \geq 3l,$$

and thus $H_{n,Q} \leq 0$, and

$$H_{n,Q} = 0 \iff \frac{S_p^*}{S_p} = \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} = \frac{E_p I_p^*}{E_p^* I_p}, \quad (p,q) \in E(CQ). \tag{2.26}$$

This implies that

$$H_n = \sum_{l=1}^{n} \sum_{Q \in \mathbf{D}(n,l)} H_{n,Q} \leq 0. \tag{2.27}$$

There are l terms in each $H_{n,Q}$, so the total number of terms contained in the sum of (2.27) is

$$\sum_{l=1}^{n} D(n,l)\, l = n^n$$

by (1.12). Therefore all n^n terms in H_n are accounted for in our regrouping (2.27).

2.3.3 LaSalle's Invariance Principle

We have shown that $\dot{V} \leq 0$ for all $(S_1, E_1, I_1, \cdots, S_n, E_n, I_n) \in \overset{\circ}{\Gamma}$, and that $\dot{V} = 0$ iff $S_k = S_k^*$ and $H_n = 0$. We claim that if $S_k = S_k^*, 1 \leq k \leq n$, then

$$H_n = 0 \iff E_k = aE_k^*, \quad I_k = aI_k^*, \quad k = 1, 2, \cdots, n, \tag{2.28}$$

where a is an arbitrary positive number. It suffices to show that $E_k/E_k^* = E_r/E_r^* = I_k/I_k^* = I_r/I_r^*$ when $\bar{\beta}_{kr} \neq 0$. By the irreducibility of (β_{ij}), $(k,r) \in E(CQ)$ for a l-cycle CQ contained in a unicyclic graph $Q \in \mathbf{D}(n,l)$ such that $\prod_{(j,h) \in E(CQ)} \bar{\beta}_{jh} \neq 0$. Therefore, from (2.26), we know $E_k/E_k^* = E_r/E_r^* = I_k/I_k^* = I_r/I_r^*$ if $H_n = 0$.

From (2.13) and (2.28), we know that $\dot{V} = 0$ iff $S_k = S_k^*, E_k = aE_k^*, I_k = aI_k^*, k = 1, 2, \cdots, n$. Substituting $S_k = S_k^*, E_k = aE_k^*$, and $I_k = aI_k^*$ into the first equation of system (2.3), we obtain

$$0 = \Lambda_k - d_k^S S_k^* - a \sum_{j=1}^{n} \beta_{kj} S_k^* I_j^*. \tag{2.29}$$

Since the right-hand-side of (2.29) is strictly decreasing in a, we know, by (2.10), that (2.29) holds iff $a = 1$, namely at P^*. Therefore, the only compact invariant subset of the set where $\dot{V} = 0$ is the singleton $\{P^*\}$. By the LaSalle Invariance Principle, P^* is globally stable in $\overset{\circ}{\Gamma}$ if $R_0 > 1$. This completes the proof of Theorem 2.3.

2.4 Summary

In this chapter, we study a class of heterogenous epidemic models – multi-group SEIR models with varying subpopulations. Starting with the seminal work by Lajmanovich and Yorke on a multi-group SIS model of Gonorrhea [87], progresses have been achieved slowly in investigating the dynamical behaviors of multi-group models during the past several decades. However, the questions of uniqueness and global stability of the endemic equilibria when the basic reproduction number is greater than 1, remain an open problem [22, 131]. In addition, most of the multi-group models in the literature are assumed to have constant subpopulations and which are not appropriate for modeling the fatal infectious diseases (e.g. HIV/AIDS). Here the population size in each group is varying.

We rigorously establish the global dynamics of the multi-group SEIR model with bilinear incidence by the graph-theoretical approach (Proposition 2.1 and Theorem 2.3). In particular, we prove the global stability of the endemic equilibrium P^* when the basic reproduction number is greater than 1 without any restriction. Biologically, our results imply that, if $R_0 \leq 1$, then the disease always dies out from all groups; if $R_0 > 1$, then the disease always persists at the unique endemic equilibrium level in all groups, irrespective of the initial conditions.

We note that other incidence forms have been used in the literature for multi-group models. The question of global stability and uniqueness of endemic equilibria for multi-group models with other forms of incidence remains open. We also point out that, for multi-group models with standard incidence, earlier results have shown [76, 131] that multiple endemic equilibria can exist when $R_0 > 1$, and hence general results on the uniqueness and global stability for standard incidence may not be expected.

The significance of this chapter is the successful use of our graph-theoretical approach to the proof of global stability of endemic equilibrium for a class of multi-group SEIR models with bilinear incidence rate. Thus a complete framework of our graph-theoretical approach is presented and illustrated by the multi-group SEIR model. At the same time, a long open problem about global stability of endemic equilibrium is resolved completely. In the next chapter, we will show another application of our graph-theoretical approach to the proof of global stability of endemic equilibrium for a class of heterogenous models: multi-stage models which is distinct from the multi-group model.

Chapter 3. Global Dynamics of a Class of Multi-Stage (MS) Models

For endemic models with long infectious period or latent period, it is reasonable to divide the long period of infectiousness or latent period into multiple stages. In this chapter, we propose a new class of heterogenous endemic model– multi-stage compartmental models to describe the transmission dynamics of infectious diseases with long infectiousness or latent period. We rigorously establish the global dynamics of the MS model using the graph-theoretical approach developed in Chapter 1.

In Section 3.1, the biological background of the multi-stage model is presented and some basic results of M-matrix are provided. In Section 3.2, the threshold quantity is calculated and the uniqueness of endemic equilibrium is shown strictly. In Section 3.3, the global stability of disease-free equilibrium is established rigorously using a Lyapunov function. The globally asymptotical stability of the endemic equilibrium when the basic reproduction number is greater than 1 is resolved completely using the graph-theoretical approach to the method of global Lyapunov functions in Section 3.4.

3.1 Modeling disease progression and amelioration through discrete stages

For infectious diseases that progress through a long infectious period, infectivity or infectiousness can vary greatly in time. The progression of a typical HIV infection can take eight to ten years before the clinical syndrome (AIDS) occurs, and the progression goes through several distinct stages, marked by drastically different $CD4^+$ T-cell counts and viral RNA levels. HIV-infected individuals are highly infectious in the first few weeks after infection, then remain in an asymptomatic stage of low infectiousness for

many years, and become gradually more infectious as their immune system becomes compromised and they progress to AIDS. Variability of infectiousness in time has been modeled in the literature by Markov chain models, or staged-progression (SP) models (see e.g. [56, 66, 72, 77, 83, 84, 100, 102, 129, 132]).

A deterministic Stage Progression (SP) model with amelioration was proposed and analyzed in [102, 58], i.e. allowing for infectives moving from more advanced stages of infection to less advantaged stages of infection. Thus current treatment can lead to both prolonging patients' lives and to increased available time for the transmission of HIV. Due to the recent HAART drug therapy advances, it is possible for infectives to move from advanced stages back to far earlier stages [102]. Also it is possible for an HIV patient to become deteriorated due to the disease development and the HIV patients could accelerate to proceed to far next stages. Based on this description about HIV patients moving in multi stages, a general multi-stage (MS) model is formulated to investigate the global dynamics in this section.

To formulate a MS model, the total host population is partitioned into the following compartments: the susceptible compartment x_1, the infectious compartment $x_i (i \geq 2)$ whose members are in the i-th stage of the disease progression, where $i = 2, \cdots, n$, and the terminal compartment T. Let δ_{ij} be the mean rate of movement or transfer from the j-th stage to the i-th stage, for $i, j = 2, \cdots, n$, and $\delta_{n+1,n}$ the mean progression rate from the n-th stage to the stage of active disease. When $i > j$, δ_{ij} represents disease progression rate; when $i < j$, δ_{ij} represents disease amelioration rate. We assume that hosts in the terminal compartment are non-infectious due to inactivity. In fact, in the case of AIDS, the terminal compartment consists of people with active AIDS. AIDS patients typically either become sexually inactive or isolated from the infection process, and their infectivity is negligible. We also assume that there is no recovery from the disease, and thus the only exit from the compartment T is death. Let β_i be the transmission coefficient for the infection of a susceptible from an infectious in the class x_i, which takes into account of average number of contact and probability of infection for each contact, then the total incidence is given by $\sum_{i=1}^{n} \beta_i x_i x_1 f(N)$, where $N = \sum_{i=1}^{n} x_i$ is the total active population. Here we assume that the density dependence of the incidence is given by a function $f(N)$ which will be specified later. A class of special interest is $f(N) = N^{-\alpha}$, $0 \leq \alpha \leq 1$, the resulting incidence term includes two of the most common incidence forms: the standard incidence form ($\alpha = 1$)

and the bilinear incidence ($\alpha = 0$). Average death rate for susceptible compartment is d_1, for the compartment x_i is d_i, which may include death due to infection, and for the active disease compartment is d_T. We assume the inflow to susceptible compartment is a constant Λ. The population transfer among compartments is schematically depicted in the Figure 3.1. All parameters in the model are assumed to be nonnegative.

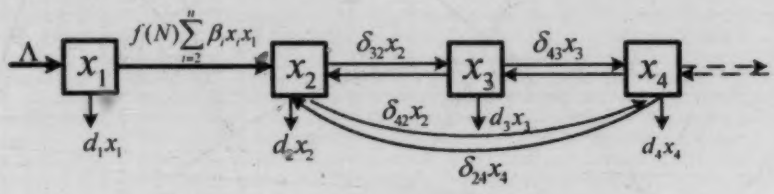


Figure 3.1: Flow diagram of a multi-stage (MS) model (3.1).

Based on our assumptions and the transfer diagram, the following system of differential equations can be derived for the multi-stage model

$$\begin{cases} \dfrac{dx_1(t)}{dt} = \Lambda - d_1 x_1 - f(N)\sum_{i=2}^{n}\beta_i x_i x_1, \\ \dfrac{dx_2(t)}{dt} = f(N)\sum_{i=2}^{n}\beta_i x_i x_1 - \left(d_2 + \sum_{r=3}^{n}\delta_{r2}\right)x_2 + \sum_{r=3}^{n}\delta_{2r}x_r, \\ \dfrac{dx_i(t)}{dt} = \sum_{r=2,r\neq i}^{n}\delta_{ir}x_r - \left(d_i + \sum_{r=2,r\neq i}^{n}\delta_{ri}\right)x_i, \qquad (i = 3,\cdots,n-1) \\ \dfrac{dx_n(t)}{dt} = \sum_{r=2,r\neq n}^{n}\delta_{nr}x_r - \left(\tilde{d}_n + \delta_{(n+1)n} + \sum_{r=2}^{n-1}\delta_{rn}\right)x_n, \end{cases} \tag{3.1}$$

and

$$\frac{dT(t)}{dt} = \delta_{(n+1)n}x_n - d_T T.$$

The incidence form is density dependent. We assume that the function $f(N)$ satisfies the following assumptions, for $N > 0$,

(H) $f(N) > 0,\ f'(N) \leq 0,\ (Nf(N))' \geq 0.$

The assumptions that $f(N) > 0$ and $f'(N) \leq 0$ are biologically motivated. As the total population N increases, the probability of a contact with a susceptible decreases, and thus the force of infection is expected to be a decreasing function of N. The other condition we impose on f is needed for our analysis. It can be verified that the class

$f(N) = N^{-\alpha}$, $0 \leq \alpha \leq 1$, satisfies (**H**). This class contains the standard incidence ($\alpha = 1$) and the bilinear incidence ($\alpha = 0$).

Let $\tilde{d}_n + \delta_{(n+1)n} = d_n$ in the n-th equation of (3.1). Also note that the 'T' equations in doesn't appear in other equations, we only need to consider the following reduced system

$$\begin{cases} \dfrac{dx_1(t)}{dt} &= \Lambda - d_1 x_1 - f(N) \displaystyle\sum_{i=2}^{n} \beta_i x_i x_1, \\ \dfrac{dx_2(t)}{dt} &= f(N) \displaystyle\sum_{i=2}^{n} \beta_i x_i x_1 - \left(d_2 + \sum_{r=3}^{n} \delta_{r2} \right) x_2 + \sum_{r=3}^{n} \delta_{2r} x_r, \\ \dfrac{dx_i(t)}{dt} &= \displaystyle\sum_{r=2, r\neq i}^{n} \delta_{ir} x_r - \left(d_i + \sum_{r=2, r\neq i}^{n} \delta_{ri} \right) x_i, \qquad (i = 3, \cdots, n) \end{cases} \tag{3.2}$$

Adding up the n equations in (3.2) we obtain

$$N' = \Lambda - d_1 x_1 - d_2 x_2 - \cdots - d_n x_n \leq \Lambda - dN.$$

where $d = \min\{d_1, \cdots d_n\}$. It follows that $\limsup_{t\to\infty} N(t) \leq \dfrac{\Lambda}{d}$. Similarly, from the first equation of (3.2) we obtain $x_1' \leq \Lambda - d_1 x_1$, and thus $\limsup_{t\to\infty} x_1(t) \leq \dfrac{\Lambda}{d_1}$. The feasible region for (3.2) can be chosen as the closed set

$$\Gamma = \{(x_1, \cdots, x_n) \in \mathbb{R}^n_+ \ : \ 0 \leq x_1 \leq \frac{\Lambda}{d_1}, \ 0 \leq x_1 + \cdots + x_n \leq \frac{\Lambda}{d}\},$$

which can be verified to be positively invariant with respect to (3.2). An equilibrium $(x_1, x_2, \cdots, x_n)$ of (3.2) satisfies

$$\begin{cases} 0 &= \Lambda - d_1 x_1 - f(N) \sum_{i=2}^{n} \beta_i x_i x_1, \\ 0 &= f(N) \sum_{i=2}^{n} \beta_i x_i x_1 - \left(d_2 + \sum_{r=3}^{n} \delta_{r2} \right) x_2 + \sum_{r=3}^{n} \delta_{2r} x_r, \\ 0 &= \displaystyle\sum_{r=2, r\neq i}^{n} \delta_{ir} x_r - \left(d_i + \sum_{r=2, r\neq i}^{n} \delta_{ri} \right) x_i, \qquad (i = 3, \cdots, n) \end{cases} \tag{3.3}$$

The disease-free equilibrium $P_0 = (\Lambda/d_1, 0, \cdots, 0)$ exists for all positive parameter values. Next we consider the existence of endemic equilibria $P^* = (x_1^*, x_2^*, \cdots, x_n^*)$, $x_i^* > 0$, $i = 1, \cdots, n$.

For the purpose of notation simplification, we let

$$-A = \begin{bmatrix} d_2 + \sum_{r=2, r\neq 2}^{n} \delta_{r2} & -\delta_{23} & \cdots & -\delta_{2n} \\ -\delta_{32} & d_3 + \sum_{r=2, r\neq 3}^{n} \delta_{r3} & \cdots & -\delta_{3n} \\ \vdots & \vdots & \ddots & \\ -\delta_{n2} & -\delta_{n3} & & d_n + \sum_{r=2, r\neq n}^{n} \delta_{rn} \end{bmatrix}. \tag{3.4}$$

The following definition and properties of M-matrices are used in our analysis. They can be found in most of the textbooks on matrix theory, see e.g. [74].

Definition of M-Matrix: $B_{n\times n}$ is a M-matrix if

(1) Off-diagonal entries of B are non-positive, and

(2) B is positively stable, namely, all eigenvalues of B have positive real parts.

Proposition 3.1. *Properties of M-matrices:*

(1) $B = \alpha I - P$, $P \geq 0$, $\alpha > \rho(P)$, the spectral radius of P.

(2) B is nonsingular and $B^{-1} \geq 0$.

(3) There exists $\beta > 0$ such that $B^{-1}x \geq \beta x$ for $x \geq 0$.

Then the following properties of the matrix A follow from the Proposition 3.1.

Proposition 3.2. *The following holds for the matrix A defined in* (3.4).

(1) $-A$ is a M-matrix.

(2) $-A^{-1}$ exists and is a non-negative matrix.

(3) There exists $\alpha > 0$ such that $-A^{-1}x \geq \alpha x$ for $x \geq 0$.

By Proposition 3.2, we know that

$$\lambda \doteq -(\beta_2, \cdots, \beta_n)A^{-1} \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} > 0, \tag{3.5}$$

which would be used to define the basic reproduction number later.

3.2 The basic reproduction number and preliminaries

Define

$$R_0 = \lambda \frac{\Lambda}{d_0} f\Big(\frac{\Lambda}{d_0}\Big), \tag{3.6}$$

which is the basic reproduction number of model (3.2). We will see this clearly in Section 3.2 and Section 3.3. If $R_0 \leq 1$, the disease dies out irrespective of the initial number of cases. If $R_0 > 1$, then the disease persists in the feasible region and there is a unique endemic equilibrium. Such a role of threshold parameter is expected of the basic reproduction number, the average number of infections caused by a single infective in a population at the disease-free equilibrium. For the interpretation of R_0, we refer the reader to [102].

Our derivation of R_0 is based on the stability analysis of the disease-free equilibrium P_0 using a Lyapunov function. Other methods of deriving R_0 exist in the literature, among them are the method of second generation matrix in [37], which was later modified in [135], and the derivation based on the linear stability analysis of P_0 (see [69]). The following Theorem 3.3 and Theorem 3.4 establish R_0 as a sharp threshold parameter. Firstly we have the following result on the number of equilibria.

Theorem 3.3. *Assume that f satisfies* (**H**). *If $R_0 \leq 1$, then P_0 is the only equilibrium in Γ. If $R_0 > 1$, then a unique endemic equilibrium P^* exists in the interior of Γ.*

Proof. The last $n-1$ equations of (3.3) can be written in the form

$$A \begin{bmatrix} x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix} = \begin{bmatrix} -f(N)\sum_{i=2}^{n} \beta_i x_i x_1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \text{ or } \begin{bmatrix} x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix} = -A^{-1} f(N) \begin{bmatrix} \sum_{i=2}^{n} \beta_i x_i x_1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}. \tag{3.7}$$

Multiplying both sides of (3.7) by the row vector $(\beta_2, \cdots, \beta_n)$, we have

$$\sum_{i=2}^{n} \beta_i x_i = (\beta_2, \cdots, \beta_n) \begin{bmatrix} x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix} = (\beta_2, \cdots, \beta_n)[-A^{-1}] f(N) \begin{bmatrix} \sum_{i=2}^{n} \beta_i x_i x_1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}.$$

Since $\sum_{i=2}^{n} \beta_i x_i \neq 0$, we obtain

$$1 = x_1 f(N)(\beta_2, \cdots, \beta_n)[-A^{-1}] \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = x_1 f(N) \lambda. \tag{3.8}$$

Also, by (3.7),

$$(1, \cdots, 1) \begin{bmatrix} x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix} = -(1, \cdots, 1) A^{-1} \cdot \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} x_1 f(N) \sum_{i=2}^{n} \beta_i x_i = p\, x_1 f(N) \sum_{i=2}^{n} \beta_i x_i, \tag{3.9}$$

where, by Proposition 3.2,

$$p \doteq -(1, \cdots, 1) A^{-1} \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} > 0. \tag{3.10}$$

From the first equation of (3.3) we get

$$x_1 f(N) \sum_{i=2}^{n} \beta_i x_i = \Lambda - d_1 x_1,$$

which, together with (3.9), implies

$$\sum_{i=2}^{n} x_i = p(\Lambda - d_1 x_1),$$

and thus

$$N = \sum_{i=1}^{n} x_i = x_1 + p(\Lambda - d_1 x_1) = p\Lambda + (1 - p d_1) x_1. \tag{3.11}$$

Substitute (3.11) into (3.8), we obtain the equation for an endemic equilibrium $(x_1, x_2, \cdots, x_n)$ to exist

$$x_1 f(p\Lambda + (1 - p d_1) x_1) = \frac{1}{\lambda}. \tag{3.12}$$

We will show that equation (3.12) has a unique positive solution in the interval $(0, \Lambda/d_0)$ when $R_0 > 1$. Let

$$g(x_1) = x_1 f(p\Lambda + (1 - p d_1) x_1).$$

Then $g(0) = 0$, and

$$g\Big(\frac{\Lambda}{d_1}\Big) = \frac{\Lambda}{d_1} f\Big(p\Lambda + (1 - pd_1)\frac{\Lambda}{d_1}\Big) = \frac{\Lambda}{d_1} f\Big(\frac{\Lambda}{d_1}\Big) = \frac{R_0}{\lambda}.$$

Furthermore, by our assumption (**H**) on function $f(N)$,

$$\begin{aligned} g'(x_1) &= f(p\Lambda + (1 - pd_1)x_1) + (1 - pd_1)x_1 f'(p\Lambda + (1 - pd_1)x_1) \\ &= f(N) + N f'(N) - p\Lambda f'(N) > 0, \end{aligned}$$

where $N = p\Lambda + (1 - pd_1)x_1$. Thus the function $y = g(x_1)$ is strictly monotonically increasing, and its graph has at most one intersection with the line $y = 1/\lambda$. Such an intersection exists for $x_1 \in (0, \Lambda/d_1)$ if and only if $g(\Lambda/d_1) > 1/\lambda$, namely, $R_0 > 1$. This completes the proof of Theorem 3.3. ∎

3.3 Global asymptotical stability of disease-free equilibrium

Theorem 3.4. *Assume that f satisfies* (**H**). *If $R_0 \leq 1$, then P_0 is globally asymptotically stable in Γ. If $R_0 > 1$, then P_0 is unstable, and system* (3.2) *is uniformly persistent with respect to Γ.*

Proof. The last $(n-2)$ equations in (3.2) can be rewritten as

$$\begin{bmatrix} x_2' \\ x_3' \\ \vdots \\ x_n' \end{bmatrix} = \begin{bmatrix} f(N)\sum_{i=2}^{n} \beta_i x_i x_1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} + A \begin{bmatrix} x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix},$$

where A is given as in (3.4). Multiplying a row vector $(c_2, c_3, \cdots, c_n)$ to the above equation, we obtain

$$(c_2, c_3, \cdots, c_n) \begin{bmatrix} x_2' \\ x_3' \\ \vdots \\ x_n' \end{bmatrix} = c_2 f(N) \sum_{i=2}^{n} \beta_i x_i x_1 + (c_2, c_3, \cdots, c_n) A \begin{bmatrix} x_2 \\ x_3 \\ \vdots \\ x_n \end{bmatrix}.$$

Choose

$$(c_2, c_3, \cdots, c_n) = -(\beta_2, \beta_3, \cdots, \beta_n)A^{-1}. \tag{3.13}$$

Since $-A^{-1}$ is nonnegative, we know $c_k \geq 0,\ k = 2, \cdots, n$. In particular,

$$c_2 = -(\beta_2, \beta_3, \cdots, \beta_n)A^{-1}\begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = \lambda > 0.$$

For the choice of c_i in (3.13), define a Lyapunov function

$$L = \sum_{k=2}^{n} c_k x_k.$$

Then, using assumption (**H**) we obtain, along a solution of (3.2),

$$\begin{aligned} L' &= c_2 f(N)x_1 \sum_{i=2}^{n} \beta_i x_i - \sum_{i=2}^{n} \beta_i x_i = (c_2 f(N)x_1 - 1)\sum_{i=2}^{n} \beta_i x_i \\ &= (\lambda f(N)x_1 - 1)\sum_{i=2}^{n} \beta_i x_i \leq (\lambda f(x_1)x_1 - 1)\sum_{i=2}^{n} \beta_i x_i \\ &\leq \Big[\lambda f\Big(\frac{\Lambda}{d_1}\Big)\frac{\Lambda}{d_1} - 1\Big]\sum_{i=2}^{n} \beta_i x_i = (R_0 - 1)\sum_{i=2}^{n} \beta_i x_i \leq 0, \quad \text{if } R_0 \leq 1. \end{aligned}$$

Furthermore, $L' = 0$ if and only if either (a) $x_2 = x_3 = \cdots = x_n = 0$ or (b) $R_0 = 1$ and $x_1 = \Lambda/d_1$ are satisfied. In either case, the largest compact invariant subset of the set

$$G = \{(x_1, x_2, \cdots, x_n) \in \Gamma \ :\ L' = 0\}$$

is the singleton $\{P_0\}$. To see this, let K be the largest compact invariant subset of G. In case (a), each solution in K satisfies equation $x_1' = \Lambda - d_1 x_1$, and the only solution that is bounded for $t \in (-\infty, +\infty)$ is $x_1 = \Lambda/d_1$. In case (b), $x_1 = \Lambda/d_1$ satisfies equation

$$x_1' = \Lambda - d_1 x_1 - [f(N)\sum_{k=2}^{n} \beta_k x_k]x_1,$$

which implies $\sum_{k=2}^{n} \beta_k x_k = 0$, i.e., $x_2 = x_3 = \cdots = x_n = 0$. Therefore, all solutions in Γ converge to P_0, by LaSalle's Invariance Principle (see [89]). The global attractivity of P_0 and the Lyapunov function L imply that P_0 is also locally stable, since otherwise P_0

will have a homoclinic orbit that is entirely contained in G, contradicting the fact that the largest compact invariant set in G is $\{P_0\}$. This establishes the global stability of P_0 when $R_0 \leq 1$.

If $R_0 > 1$, $L' > 0$ for x_1 sufficiently close to Λ/d_1, and thus solutions in Γ sufficiently close to P_0 move away from P_0, except those on the invariant x_1-axis, along which solutions converge to P_0. Therefore, P_0 is unstable. Furthermore, $\{P_0\}$ is the only compact invariant set on the boundary of Γ and is isolated. The local dynamics near P_0 and the boundary of Γ imply that system (3.2) is uniformly persistent (see [19]) with respect to Γ, when $R_0 > 1$. The proof of uniform persistence of (3.2) is similar to that of Proposition 3.3 in [92].

■

3.4 Global asymptotical stability of endemic equilibrium

In this section, for $f(N) \equiv 1$, we prove the global stability of the endemic equilibrium P^* when $R_0 > 1$ using the global Lyapunov function and the graph-theoretical approach we developed earlier. Again we demonstrate that the use of graph-theoretical approach can greatly simplify the proof for high-dimensional systems.

Theorem 3.5. *Assume that $f(N) \equiv 1$ and $R_0 > 1$. Then the endemic equilibrium P^* is globally asymptotically stable in the interior of Γ.*

The endemic equilibrium equations are

$$\begin{cases} 0 = \Lambda - d_1 x_1^* - \sum_{i=2}^{n} \beta_i x_i^* x_1^*, \\ 0 = \sum_{i=2}^{n} \beta_i x_i^* x_1^* - \left(d_2 + \sum_{r=2, r\neq 2}^{n} \delta_{r2} \right) x_2^* + \sum_{r=2, r\neq 2}^{n} \delta_{2r} x_r^*, \\ 0 = \sum_{r=2, r\neq i}^{n} \delta_{ir} x_r^* - \left(d_i + \sum_{r=2, r\neq i}^{n} \delta_{ri} \right) x_i^*, \qquad (i = 3, \cdots, n) \end{cases} \tag{3.14}$$

Let $x = (x_1, x_2, \cdots, x_n)$. Consider a global Lyapunov function

$$V(x) = \sum_{i=1}^{n} v_i \left(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*} \right),$$

where v_i are positive constants which would be specified later, and x_i^* is the component of endemic equilibrium P^*. The derivative of $V(x)$ along the solution $x(t)$ is

$$\frac{dV(x)}{dt} = \sum_{i=1}^{n} v_i \left(1 - \frac{x_i^*}{x_i}\right) \frac{dx_i}{dt}. \tag{3.15}$$

Using $\Lambda = d_1 x_1^* + \sum_{i=2}^{n} \beta_i x_1^* x_i^*$, the first endemic equilibrium equation, we have

$$\begin{aligned}
\left(1 - \frac{x_1^*}{x_1}\right) \frac{dx_1}{dt} &= \Lambda - d_1 x_1 - \sum_{i=2}^{n} \beta_i x_1 x_i - \Lambda \frac{x_1^*}{x_1} + d_1 x_1^* + \sum_{i=2}^{n} \beta_i x_1^* x_i \\
&= d_1 x_1^* \left(2 - \frac{x_1}{x_1^*} - \frac{x_1^*}{x_1}\right) - \sum_{i=2}^{n} \beta_i x_1 x_i + \sum_{i=2}^{n} \beta_i x_1^* x_i \\
&+ \sum_{i=2}^{n} \beta_i x_1^* x_i^* - \sum_{i=2}^{n} \beta_i x_1^* x_i \frac{x_1^*}{x_1} \\
&\leq \sum_{i=2}^{n} \beta_i x_1^* x_i - \sum_{i=2}^{n} \beta_i x_1 x_i + d_1 x_1^* \left(2 - \frac{x_1}{x_1^*} - \frac{x_1^*}{x_1}\right) \\
&+ \sum_{i=2}^{n} \beta_i x_1^* x_i^* - \sum_{i=2}^{n} \beta_i x_1^* x_i^* \frac{x_1^*}{x_1}.
\end{aligned} \tag{3.16}$$

Similarly we have

$$\begin{aligned}
&\left(1 - \frac{x_2^*}{x_2}\right) \frac{dx_2}{dt} \\
&= \sum_{i=2}^{n} \beta_i x_1 x_i - \left(d_2 + \sum_{r=2, r\neq 2}^{n} \delta_{r2}\right) x_2 + \sum_{r=2, r\neq 2}^{n} \delta_{2r} x_r \\
&- \sum_{i=2}^{n} \beta_i x_1 x_i \frac{x_2^*}{x_2} + \left(d_2 + \sum_{r=2, r\neq 2}^{n} \delta_{r2}\right) x_2^* - \sum_{r=2, r\neq 2}^{n} \delta_{2r} x_r \frac{x_2^*}{x_2}.
\end{aligned} \tag{3.17}$$

For $i = 3, \cdots, n$, we obtain

$$\begin{aligned}
\left(1 - \frac{x_i^*}{x_i}\right) \frac{dx_i}{dt} &= \sum_{r=2, r\neq i}^{n} \delta_{ir} x_r - (d_i + \sum_{r=2, r\neq i}^{n} \delta_{ri}) x_i \\
&- \sum_{r=2, r\neq i}^{n} \delta_{ir} x_r \frac{x_i^*}{x_i} + (d_i + \sum_{r=2, r\neq i}^{n} \delta_{ri})(x_i)^*.
\end{aligned} \tag{3.18}$$

Substitute (3.16), (3.17) and (3.18) into (3.15), we obtain

$$\begin{aligned}\frac{dV(x)}{dt} &= (v_2 - v_1)\sum_{i=2}^{n}\beta_i x_1 x_i + v_1\sum_{i=2}^{n}\beta_i x_1^* x_i \\ &+ \sum_{i=2}^{n} v_i\left(\sum_{r=2,r\neq i}^{n}\delta_{ir}x_r - (d_i + \sum_{r=2,r\neq i}^{n}\delta_{ri})x_i\right) \\ &+ v_1\sum_{i=2}^{n}\beta_i x_1^* x_i^* + \sum_{i=2}^{n} v_i(d_i + \sum_{r=2,r\neq i}^{n}\delta_{ri})x_i^* \\ &- v_1\sum_{i=2}^{n}\beta_i x_1^* x_i^*\frac{x_1^*}{x_1} - v_2\sum_{i=2}^{n}\beta_i x_1 x_i\frac{x_2^*}{x_2} - \sum_{i=2}^{n} v_i \sum_{r=2,r\neq i}^{n}\delta_{ir}x_r\frac{x_i^*}{x_i} \\ &+ v_1 d_1 x_1^*\left(2 - \frac{x_1}{x_1^*} - \frac{x_1^*}{x_1}\right).\end{aligned} \tag{3.19}$$

We choose v_i so that the following holds

$$\begin{aligned}(v_2 - v_1) &= 0, \\ v_1\sum_{i=2}^{n}\beta_i x_1^* x_i + \sum_{i=2}^{n} v_i\left(\sum_{r=2,r\neq i}^{n}\delta_{ir}x_r - (d_i + \sum_{r=2,r\neq i}^{n}\delta_{ri})x_i\right) &= 0,\end{aligned} \tag{3.20}$$

for all nonnegative values of $x_i, i = 1, \cdots, n$. This is equivalent to the following linear system

$$\begin{aligned}(v_2 - v_1) &= 0, \\ \beta_2 x_1^* v_1 + \sum_{i=2,i\neq 2}^{n-1}\delta_{i2}v_i - \left(d_2 + \sum_{r=2,r\neq 2}^{n}\delta_{r2}\right)v_2 &= 0, \\ &\cdots \\ \beta_n x_1^* v_1 + \sum_{i=2,i\neq n}^{n}\delta_{in}v_i - \left(d_n + \sum_{r=2,r\neq n}^{n}\delta_{rn}\right)v_n &= 0.\end{aligned} \tag{3.21}$$

Multiplying the i-th equation by $x_i^*(i = 2, \cdots, n)$, we obtain

$$\begin{aligned}(v_2 - v_1)\sum_{i=2}^{n}\beta_i x_i^*\, x_1^* &= 0, \\ v_1\beta_2 x_2^* x_1^* + \sum_{i=2,i\neq 2}^{n} v_i\delta_{i2}x_2^* &= v_2\left(d_2 + \sum_{i=2,i\neq 2}^{n}\delta_{i2}\right)x_2^*, \\ &\cdots \\ v_1\beta_n x_n^* x_1^* + \sum_{i=2,i\neq n}^{n} v_i\delta_{in}x_n^* &= v_n\left(d_n + \sum_{i=2,i\neq n}^{n}\delta_{in}\right)x_n^*.\end{aligned} \tag{3.22}$$

For the last $N-1$ equations in (3.14), multiply $v_2, v_3, \cdots, v_n$ both sides, we get

$$\begin{aligned} v_2 \sum_{i=2}^{n} \beta_i x_i^* x_1^* + v_2 \sum_{r=2, r\neq 2}^{n} \delta_{2r} x_r^* &= v_2 \left(d_2 + \sum_{r=2, r\neq 2}^{n} \delta_{r2} \right) x_2^*, \\ v_3 \sum_{r=2, r\neq 3}^{n} \delta_{3r} x_r^* &= v_3 \left(d_3 + \sum_{r=2, r\neq 3}^{n} \delta_{r3} \right) x_3^*, \\ &\cdots \\ v_n \sum_{r=2, r\neq n}^{n} \delta_{nr} x_r^* &= v_n \left(d_n + \sum_{r=2, r\neq n}^{n} \delta_{rn} \right) x_n^*. \end{aligned} \tag{3.23}$$

Substituting (3.23) into (3.22), we obtain

$$\begin{aligned} (v_2 - v_1) \sum_{i=2}^{n} \beta_i x_i^* \, x_1^* &= 0, \\ v_2 \sum_{i=2}^{n} \beta_i x_i^* x_1^* + v_2 \sum_{r=2, r\neq 2}^{n} \delta_{2r} x_r^* &= v_1 \beta_2 x_2^* x_1^* + \sum_{i=2, i\neq 2}^{n} v_i \delta_{i2} x_2^*, \\ v_3 \sum_{r=2, r\neq 3}^{n} \delta_{3r} x_r^* &= v_1 \beta_3 x_3^* x_1^* + \sum_{i=2, i\neq 3}^{n} v_i \delta_{i3} x_3^*, \\ &\cdots \\ v_n \sum_{r=2, r\neq n}^{n} \delta_{nr} x_r^* &= v_1 \beta_n x_n^* x_1^* + \sum_{i=2, i\neq n}^{n} v_i \delta_{in} x_n^* \end{aligned} \tag{3.24}$$

Rewriting above system about variables $v_1,\ v_2, \cdots v_n$, we get a linear system

$$\begin{bmatrix} \sum_{i=2}^{n} \beta_i x_i^* x_1^* & -\sum_{i=2}^{n} \beta_i x_i^* x_1^* & 0 & \cdots & 0 \\ -\beta_2 x_2^* x_1^* & \sum_{i=2}^{n} \beta_i x_i^* x_1^* + \sum_{\substack{r=2 \\ r\neq 2}}^{n} \delta_{2r} x_r^* & -\delta_{32} x_2^* & \cdots & -\delta_{n2} x_2^* \\ -\beta_3 x_3^* x_1^* & -\delta_{23} x_3^* & \sum_{\substack{r=2 \\ r\neq 3}}^{n} \delta_{3r} x_r^* & & -\delta_{n3} x_3^* \\ \vdots & \vdots & & \ddots & \\ -\beta_n x_n^* x_1^* & -\delta_{2n} x_n^* & -\delta_{3n} x_n^* & & \sum_{\substack{r=2 \\ r\neq n}}^{n} \delta_{nr} x_r^* \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ \vdots \\ v_n \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}. \tag{3.25}$$

Let

$$\begin{aligned} &\bar{\beta}_{12} = \sum_{i=2}^{n} \beta_i x_i^* x_1^*; && \bar{\beta}_{1i} = 0, \quad i = 3, \cdots, n, \\ &\bar{\beta}_{i1} = \beta_i x_i^* x_1^*, \quad i = 2, \cdots, n; && \bar{\beta}_{ij} = \delta_{ji} x_i^*, \quad i, j = 2, \cdots, n, \quad i \neq j. \end{aligned} \tag{3.26}$$

Thus all $\bar{\beta}_{ij} \geq 0$ and there is a relationship

$$\bar{\beta}_{12} = \sum_{i=2}^{n} \bar{\beta}_{i1}. \tag{3.27}$$

The linear algebraic system (3.25) is converted to the standard form of (1.2). The coefficient matrix is irreducible and has the property that the sum of each column equals to zero. By Proposition 1.3, the solution space of system (3.25) has dimension 1 and a basis of the solution space is given by

$$v_k = \sum_{T \in \mathbb{T}_k} \prod_{(j,h) \in E(T)} \bar{\beta}_{jh} > 0, \quad k = 1, \cdots, n,$$

where $\mathbb{T}_k$ is the set of all directed n-trees rooted at the k-th vertex, and $E(T)$ denotes the set of directed arcs in a directed n-tree T. With v_k determined in this way, (3.20) always holds and (3.19) reduces to

$$\begin{aligned} \frac{dV(x)}{dt} \leq\ & v_1 \sum_{i=2}^{n} \beta_i x_1^* x_i^* + \sum_{i=2}^{n} v_i \Big(d_i + \sum_{r=2, r \neq i}^{n} \delta_{ri} \Big) x_i^* \\ & - v_1 \sum_{i=2}^{n} \beta_i x_1^* x_i^* \frac{x_1^*}{x_1} - v_2 \sum_{i=2}^{n} \beta_i x_1 x_i \frac{x_2^*}{x_2} - \sum_{i=2}^{n} v_i \sum_{r=2, r \neq i}^{n} \delta_{ir} x_r \frac{x_i^*}{x_i}, \end{aligned} \tag{3.28}$$

since $v_1 d_1 x_1^* \left(2 - \frac{x_1}{x_1^*} - \frac{x_1^*}{x_1} \right) \leq 0$. From the first equation in (3.22) we know that $v_1 = v_2$. Sum up all equations in (3.23), we get

$$v_2 \sum_{i=2}^{n} \beta_i x_i^* x_1^* + \sum_{i=2}^{n} v_i \sum_{r=2, r \neq i}^{n} \delta_{ir} x_r^* = \sum_{i=2}^{n} v_i \Big(d_i + \sum_{r=2, r \neq i}^{n} \delta_{ri} \Big) x_i^*. \tag{3.29}$$

Substituting (3.29) into (3.28), we obtain

$$\begin{aligned} \frac{dV(x)}{dt} \leq\ & v_2 \sum_{i=2}^{n} \beta_i x_1^* x_i^* - v_1 \sum_{i=2}^{n} \beta_i x_1^* x_i^* \frac{x_1^*}{x_1} + v_1 \sum_{i=2}^{n} \beta_i x_1^* x_i^* - v_1 \sum_{i=2}^{n} \beta_i x_1 x_i \frac{x_2^*}{x_2} \\ & + \sum_{i=2}^{n} v_i \sum_{\substack{r=2 \\ r \neq i}}^{n} \delta_{ir} x_r^* - \sum_{i=2}^{n} v_i \sum_{\substack{r=2 \\ r \neq i}}^{n} \delta_{ir} x_r \frac{x_i^*}{x_i}. \end{aligned} \tag{3.30}$$

Using the definition in (3.26) and (3.27), we have

$$\begin{aligned}
\frac{dV(x)}{dt} &\le v_2 \sum_{i=2}^{n} \bar{\beta}_{i1}\Big(1 - \frac{x_1^*}{x_1}\Big) + v_1 \sum_{i=2}^{n} \bar{\beta}_{i1}\Big(1 - \frac{x_1}{x_1^*}\frac{x_i}{x_i^*}\frac{x_2^*}{x_2}\Big) + \sum_{i=2}^{n} v_i \sum_{\substack{r=2\\ r\neq i}}^{n} \bar{\beta}_{ri}\Big(1 - \frac{x_r}{x_r^*}\frac{x_i^*}{x_i}\Big) \\
&= v_2\bar{\beta}_{12}\Big(1 - \frac{x_1^*}{x_1}\Big) + v_1 \sum_{i=2}^{n} \bar{\beta}_{i1}\Big(1 - \frac{x_1}{x_1^*}\frac{x_i}{x_i^*}\frac{x_2^*}{x_2}\Big) \\
&\quad + v_2 \sum_{\substack{r=2\\ r\neq 2}}^{n} \bar{\beta}_{r2}\Big(1 - \frac{x_r}{x_r^*}\frac{x_2^*}{x_2}\Big) + \sum_{i=3}^{n} v_i \sum_{\substack{r=2\\ r\neq i}}^{n} \bar{\beta}_{ri}\Big(1 - \frac{x_r}{x_r^*}\frac{x_i^*}{x_i}\Big) \\
&= v_1 \sum_{i=2}^{n} \bar{\beta}_{i1}\Big(1 - \frac{x_1}{x_1^*}\frac{x_i}{x_i^*}\frac{x_2^*}{x_2}\Big) \\
&\quad + v_2\bar{\beta}_{12}\Big(1 - \frac{x_1^*}{x_1}\Big) + v_2 \sum_{r=3}^{n} \bar{\beta}_{r2}\Big(1 - \frac{x_r}{x_r^*}\frac{x_2^*}{x_2}\Big) \\
&\quad + \sum_{i=3}^{n} v_i \sum_{\substack{r=2\\ r\neq i}}^{n} \bar{\beta}_{ri}\Big(1 - \frac{x_r}{x_r^*}\frac{x_i^*}{x_i}\Big).
\end{aligned} \tag{3.31}$$

Define

$$\begin{aligned}
H_n(x) &= v_1 \sum_{i=2}^{n} \bar{\beta}_{i1}\Big(1 - \frac{x_1}{x_1^*}\frac{x_i}{x_i^*}\frac{x_2^*}{x_2}\Big) + v_2\Big[\bar{\beta}_{12}\Big(1 - \frac{x_1^*}{x_1}\Big) + \sum_{r=3}^{n} \bar{\beta}_{r2}\Big(1 - \frac{x_r}{x_r^*}\frac{x_2^*}{x_2}\Big)\Big] \\
&\quad + \sum_{i=3}^{n} v_i \sum_{\substack{r=2\\ r\neq i}}^{n} \bar{\beta}_{ri}\Big(1 - \frac{x_r}{x_r^*}\frac{x_i^*}{x_i}\Big),
\end{aligned} \tag{3.32}$$

where $x = (x_1, \cdots, x_n)$. It remains to prove that $H_n \le 0$.

Observe that, as in the case of multigroup models, v_k satisfies system (1.2), and thus expansions of $v_k\bar{\beta}_{jk}$ in (3.32) have products represented by unicyclic n-digraphs. Re-grouping the terms in $H_n(x)$ according the unicyclic graphs, as in Section 2.3.2, we can show $H_n(x) \le 0$ for all nonnegative values of x.

The set $\{x \in \Gamma \mid H_n(x) = 0\}$ can be similarly characterized to show that it has $\{P^*\}$ as the largest compact invariant set. Therefore the global stability of P^* follows from the LaSalle's Invariance Principle.

3.5 Summary

In this chapter, we consider a multi-stage endemic model with amelioration and rigorously establish its global dynamics. The proof of the global stability of the endemic equilibrium uses our graph-theoretical approach to the method of global Lyapunov functions developed in Chapter 1.

Models for the spread of HIV/AIDS often incorporate staged progression where an individual may proceed through several distinct infective stages before developing full AIDS [77, 98]. Sometimes these stages are meant to correspond to T4 cell count ranges [71, 98]. With recent advances in drug therapies (HAART), it is necessary to consider amelioration where individuals may move from more advanced stages of infection to less advanced stages. It is also reasonable to incorporate HIV infection deterioration due to other causes. Thus the multi-stage model containing all these considerations is appropriate to be used to study the transmission dynamics of disease progression in a host population, for example HIV infection.

Actually, the multi-stage (MS) model (3.1) is a generalization of many epidemic models with multiple stages in the literature: including a stage-progression model in [77], and a stage-progression model with amelioration in [102]. The MS model (3.1) also contains the classical SEIR and SIR models when $n = 3$ and 2, respectively. In such cases, a latent class can be regarded as an infectious stage with infection coefficient equals to 0. In [103], a $SE_1E_2\cdots E_{n-2}IR$ model was proposed to model the long latent period. The model is a special case of our MS model with $\beta_i = 0, i = 2, \cdots, n-1$. Our results of the MS model contain those established in [56, 58]. However, it is an impossible task to prove the global stability of endemic equilibrium of our MS model using the technique, partition of unity.

The significance of this chapter is that our graph-theoretical approach can be used to prove the global stability of the endemic equilibrium P^* when $R_0 > 1$ for a class of heterogenous endemic multi-stage models. Thus it is expected that our graph-theoretical approach has a wide applicability to deal with the global stability of endemic equilibria for a large-scale class of epidemic models with bilinear incidence.

Part 2. Mathematical Modeling of Transmission Dynamics of *Mycobacterium* Tuberculosis

Tuberculosis (TB) is an ancient infectious disease and continues to be a major global threat to public health today. According to the 2007 WHO TB Report [140], an estimated 1.6 million people died of TB and 8.8 million new TB cases occurred in 2005, of which 7.4 million in Asia and sub-Saharan Africa. It is estimated that one-third of the world's population (2 billion) are infected with TB [141], most of which occur in developing countries in sub-Sahara Africa and south-east Asia. After HIV, TB is the greatest infectious killer of youth and adults in the world today.

Over the past several decades, there has been a sharp reduction in the incidence rate and death rate of TB in most developed countries [62, 63, 64, 79, 128]. Such countries include, for example, Australia, Canada, Denmark, Netherlands, New Zealand, Norway, Sweden, the United States and the UK etc. In most of these immigration countries, the foreign-born population has contributed most of active TB cases and maintained a high TB incidence rate. The TB incidence rate of local-born population has maintained a declining trend and at a lower level. Data from the UK [63, 64], however, is showing a different trend: the local-born population maintains a constant TB incidence rate and the foreign-born has a increasing trend for the TB incidence rate.

In Chapter 5, we propose a three-population TB model to investigate the impact of cross-infection on TB incidence of local-born population in immigration countries, and the effects of foreign-born population on overall TB incidence in an immigration country. After establishing the qualitative behaviors, we investigate quantitatively the detailed impact of those factors on TB incidence in Chapter 6 by two case studies in Canada and the UK. Our model can explain both countries' TB trends.

Since early and late latent TB have high and low risk to develop active TB, we investigate the impact of annual new immigrants with early and late latent TB on the incidence rate in immigration countries in Chapter 7. TB doesn't have permanent immunity, we study the effects of partial immunity and relapses of TB on the basic reproduction number and TB incidence in a high TB incidence country – South Africa in Chapter 8.

Chapter 4. Introduction

In this chapter, we first give a brief history of TB, followed by a brief introduction to basic epidemiology of TB. We will also discuss previous TB studies using compartmental models.

4.1 A brief history of Tuberculosis

Evidence of tuberculosis in humans dates back to at least 8,000 B.C., documented in prehistoric skeletal remains in Germany and Peru. The disease has also been found in ancient Egyptian mummies [31]. Due to the high fatality, tuberculosis had been known historically as "consumption" and "white plague". TB was responsible for at least one billion deaths during the nineteenth and early twentieth century [24].

For centuries, it was not clear how TB was transmitted until the German scientist Robert Koch, discovered the causative agent (organism) - *tubercle bacillus* in 1882. In 1952, Isoniazid (INH) was first used to treat TB patients which indicated the beginning of chemotherapy using antibiotics. Most countries have undergone sharp decreases in both active TB cases and TB deaths since 1950s until this trend halted during late 1990s in United States and other countries [114].

Tuberculosis was declared a 'global emergency' by the World Health Organization (WHO) in 1993. In 1995, a comprehensive plan – Directly Observed Therapy and short course (DOTS) plan to stop tuberculosis spread globally was launched by WHO. By 2005, DOTS plan has been implemented in 187 countries and an estimated 60% of new smear-positive cases were treated under DOTS [140]. Though great progress has been made under the DOTS plan in TB control globally, new factors continue to challenge the current control measures. International migration accelerates the global spread of TB from high TB incidence countries to low TB incidence countries and changes the transmission dynamics in developed countries ultimately [62, 79, 128].

Other continuing challenges of TB control are: inadequate diagnostics and treatment; limited access to DOTS program; Multi-drug resistant TB (MDR-TB) and HIV co-infection and global spread of TB [114]. The Global Plan to Stop TB (2006 - 2015) is implemented to achieve the target: to reduce TB incidence, TB prevalence and death rates by 50% (relative to 1990) by 2015.

4.2 Basic epidemiology of TB and earlier works on mathematical modeling

Tuberculosis is caused by *Mycobacterium tuberculosis*. It spreads from person to person by inhalation of droplets containing the *tubercle bacillus*, expelled by infectious persons with active tuberculosis when they coughs, sneezes or talks. TB usually infects the lungs but can affect other organs of the body, such as the lymph nodes, the bones and (rarely) the brain. The disease in the lungs is called *pulmonary* tuberculosis and those not in the lungs are called *extra pulmonary* tuberculosis [42]. Only individuals with pulmonary TB are infectious and those with extra pulmonary TB are not infectious.

Mathematical models have been developed to study TB relatively late compared to other diseases (possibly since TB is curable due to available chemotherapy) [24]. The first TB transmission model was proposed by Waaler *et al* in 1962 [138] using discrete equations for TB in India. After that many other TB models have been proposed and most of which are statistical models (see recent survey [24] for mathematical modeling of TB). Blower *et al* [13, 14, 117] considered the intrinsic transmission dynamics of tuberculosis using mathematical models with two routes to active TB – fast route and slow route, which are typical characters of TB progression. They used these models to investigate the historical decline of TB incidence and deaths in Europe and the United States before the antibiotics.

Infection with *M. tuberculosis* does not necessarily lead to tuberculosis. Most people who are infected with TB carry the bacterium without showing any symptom and are said to be in latent stage. The latency is variable from a couple of months to many years. People with latent TB are not infectious and cannot transmit tuberculosis. Approximately 10% of people with latent TB who are not given preventive therapy will develop active TB disease. Half will become ill within the first 2 years of infection, while the other half will develop active TB at some point later in their lives. Feng

et al considered the effects of long and variable latent period to the TB dynamics in [46]. In [143], a TB model with early and late latent stage TB was explored to assess the effects of different treatment strategies for treatment of patients with early or late latent TB. Castillo-Chavez and Song [125] considered the fast and slow dynamics due to the different epidemiological time scales, short TB infectiousness period and long and slow TB period of progression. Changes from environmental, demographic and social conditions would also lead to alter the dynamics of evolution of TB strains [3]. Most cases of active TB are the result of reactivation of an endogenous infection. Left untreated, each person with active TB disease will infect on average between 10 and 15 people every year [140]. In [137], Vynnycky *et al* used a partial differential equations model to explore the effects of endogenous reactivation, exogenous reinfection and BCG vaccination.

Inconsistent or partial treatment has resulted in *multi-drug resistant tuberculosis* (MDR-TB) which is defined to be resistant to at least isoniazid and rifampicin [140]. Though MDR-TB is generally treatable, the drug regime is quite expensive and toxic [114, 140]. Castillo-Chavez and Feng [23, 45] considered one or two-strain TB models to study the mechanisms of survival and spread of naturally resistant strains of TB and antibiotic-generated resistant strains of TB. Due to the partial (incomplete or temporary) immunity of TB, exogenous reinfection or relapses of TB are not rare in high TB incidence areas. The impact of exogenous reinfection of TB is investigated by both Feng *et al* [44] and Chiang *et al* [27, 44]. In this thesis, we will investigate the impact of partial immunity and relapses on the TB incidence rate and basic reproduction number in Chapter 7.

People infected with HIV are at a much higher risk of progressing to active TB than those without them. Thus co-infection with HIV may have significant impact on TB dynamics. Kirschner [83] studied the dynamics of co-infection with tuberculosis and HIV-1. Current research on this topic has been intensified not only on its dynamical behaviors but the potential benefits for TB-HIV control.

Two of the most important challenges for TB modeling raised in [24] are immigration and ethnicity. Murphy *et al* [112] compared the TB epidemic in demographically distinct heterogenous populations between India and USA to investigate the effects of host genetics. McCluskey and van den Driessche considered a TB model with latent and infective immigration to the population [104]. Global spread by migration and/or

air travel from high TB incidence countries to low TB incidence countries poses a new challenge to TB control in developed countries. In [113], the author considered the dynamics of tuberculosis transmission among foreign-born people from a point of view of molecular epidemiology. To my best knowledge, there is no published works in the literature that investigate the effects of migration and cross-infection on the TB incidence rate using compartmental models.

In the next chapter, we propose a three-population TB model to investigate the impact of migration from developing countries to developed countries on the TB incidence in the developed countries. One population represents that of a developing country, the other two populations represent those of immigrant and local-born in a developed country. We assume that a fraction of immigrants from the developing country are latently infected with TB, so they will directly influence the TB incidence in the immigrant population. We also assume that there is cross-infection from the immigrant population to the local-born population, so the new immigrants with latent TB will also indirectly influence the TB incidence of the local-born population.

The model will be used to evaluate the impacts of the fraction of the new immigrants who have latent TB, and the level of cross-infection from immigrant population to the local-born population. In Chapter 5, we rigorously establish the global dynamics of the three-population model and derive the basic reproduction number.

In Chapter 6, the model is used to explain the TB data in Canada and the UK, using numerical simulations. Our analysis demonstrate that, if the TB incidence rate in the immigrant population is low, as in the case of Canada (19.4 per 100,000 population), then the cross-infection from immigrants to local-born population has little effect, and latent TB through new immigrant only affects the TB incidence of the immigrant population. However, if the TB incidence rate in the immigrant population is sufficiently high, as in the case of the UK (103.3 per 100,000), then the effects of cross-infection can be very serious, and latent TB brought in by new immigrants will not only increase the TB incidence rates among immigrants, but also alter the TB trend in the local-born population.

From a public health viewpoint, our results suggest that it is necessary for Canada to maintain the strict screening of TB among new immigrants, to keep the TB incidence among immigrant population at a low level. This will reduce the damage caused by cross-infection from foreign-born to local-born population.

In Chapters 7 and 8, we develop mathematical models to investigate the effects of TB latency and TB immunity.

Chapter 5. Impact of Immigration on TB Incidence

In a number of developed countries with substantial levels of immigration, foreign-born population becomes a major force that increasingly contributes to the national TB incidence [62, 63, 64, 79]. A recent trend can be clearly observed in the TB data in most immigration countries: the overall TB incidence rates are on the decline, an increasingly greater proportion of the TB cases comes from the immigrant population. TB incidence of foreign-born population remains at a high constant level, and TB incidence of local-born population remains low and is on the decline. However the TB data from the UK shows a different trend. Since 2000, TB incidence among non-UK borns keeps increasing, and TB incidence among UK-borns remains at a constant level [63, 64]. Why does the TB incidence rate of the UK-born population show a constant instead of a declining trend as in other immigration countries? It has been suggested in UK government studies [63, 64] that cross-infection from non-UK born to UK-born may be a key factor. The effects of cross-infection of TB from foreign-born population to local-born population have been investigated in several studies [62, 78, 97, 107, 113]. However, the results are mixed and far from conclusive. A study by Dasgupta and Menzies [35] has revealed that, among developed countries, the proportion of active TB cases among the local-born that can be attribute to transmission from the foreign-born ranges from as low as 2% to as high as 17%. Recent studies using DNA fingerprint techniques have confirmed significant cross-infection in Spain [78] and the Netherland [15], but not in Norway [34] and Denmark [97].

In this chapter, we propose a three-population TB model with immigration and cross-infection to describe the transmission dynamics due to global spread of TB from high TB incidence countries to low TB incidence countries. The main purpose of this chapter is to rigorously establish the global dynamics of our model. This model will be

used in Chapter 6 to investigate the impact of latent TB cases among new immigrants on the TB incidence of the foreign-born population, and the effects of cross-infection on the TB incidence rate of local-born population. Our TB model can explain both TB trends in the UK and other immigration countries.

In Sections 5.1 and 5.2, we present the TB data and summarize the common trend and possible causes. In Section 5.3, we propose our TB model with migration and cross-infection. In Section 5.4, the strategy for model analysis for proof is explained. In Sections 5.5 – 5.7, we establish the global dynamics for the limiting subsystems and then global behaviors for our full model using the theory of asymptotically autonomous systems. The proof of global stability of endemic equilibrium is given in Appendix A.

5.1 Introduction

Among the annual notified active TB cases from foreign-born, 20% more are discovered at arrival and many develop the disease several years of post-immigration [79]. It is reasonable to assume that a large proportion of immigrants have latent tuberculosis infection (LTBI) pre-immigration. Thus strategies for the control and elimination of TB among foreign-born population are at highest need in the public health sectors in these countries. From view point of molecular epidemiology, foreign-born people are more likely to be infected in their country of origin and then either primary disease develops shortly after immigration or the people remain at risk for reactivated disease for the rest of their lives [113]. It is also plausible that TB transmission within immigrant communities in the host country is common [63]. In [79, 113], it is estimated that there is almost half of immigrants who got recent TB infection within community. Also the cross infection is not very rare between immigrants and their next generation or other local-born persons [63, 64, 79].

Migration from countries with high TB incidence and prevalence to countries with low TB incidence and prevalence has increased during the last couple of decades and would continue to increase in the future. Most immigrants come from developing countries and it seems impossible to neglect the impact posed by immigrants in every immigration country. Figure 5.1 shows a diagram of migration between developed countries and developing countries and interaction among populations in immigration countries. Among most developed countries with immigration policies, a recent trend

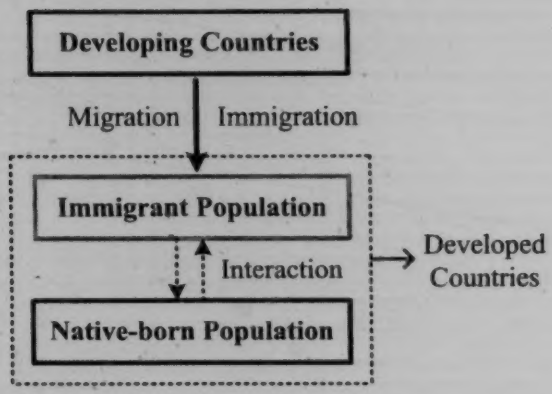


Figure 5.1: Migration from developing countries to developed countries and interaction between immigrant and local-born populations in developed countries.

Groups in Australia	Proportion in total population	Proportion of TB Cases	Incidence rate cases per 100,000
Oversea-born	25.5%	82.3%	21.7
Non-indigenous	72.5%	13.98%	1.0
Indigenous	2%	3.72%	8.1
Total	20,111,300	1,076	5.4

Table 5.1: Australia 2005 TB data summary.

can be clearly observed in the TB data: while the overall TB incidence rates are on the decline, an increasingly greater proportion of the TB cases comes from the immigrant population.

5.2 Trends in TB data from developed countries

In Table 5.1, a summary of 2004 Australia TB data is given [79]. The data comes from "Tuberculosis notifications in Australia, 2005", annual report of Communicable Diseases Network Australia. We see from the data that the oversea-born population has a much higher TB incidence rate (21.7 per 100,000 persons per year) and contributes a majority (82.3%) of the overall TB cases in 2005.

In Canada, since 1970, a steady increase of the proportion of TB cases contributed

Groups in Canada	Proportion in total population	Proportion in TB Cases	Incidence rate cases per 100,000
Foreign-born	19%	67%	19.4
Non-aboriginal	77%	16%	1.0
Aboriginal	4%	15%	23.3
Total	100%	98%	5.2

Table 5.2: Canada 2002 TB data summary (PHAC).

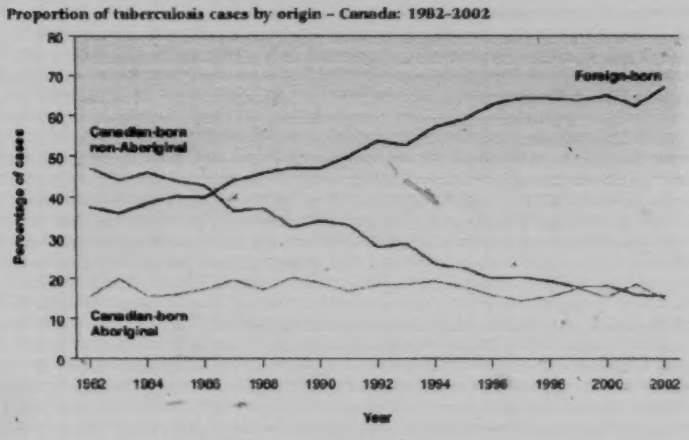


Figure 5.2: Percentage of TB cases by origin in Canada from 1982-2002 (PHAC).

by foreign-born population has been noted, see Figure 5.2 [62]. TB incidence rate among the foreign-born population remains to be high and relatively constant while the incidence rate among the Canadian-born population is on the decline, see Figure 5.3. Table 5.2 is a summary of Canada TB data in 2002. Data comes from annual report "Tuberculosis in Canada 2001" by Public Health Agency of Canada (PHAC).

In the Netherlands, the proportion of TB patients with a non-Dutch passport rose from approximately 35% in 1980 to almost 60% in 1997 [142]. In Norway, two thirds of the TB cases were discovered in immigrants [43]. In mid-1970's, the proportion of immigrants in total population is 2.4% and TB cases contributed by immigrants constitutes 4%. In 2002, those two figures increase to 6.9% and 76%, respectively. In 2002, TB incidence rate among Norway-born population is 1.4 (per 100,000 persons)

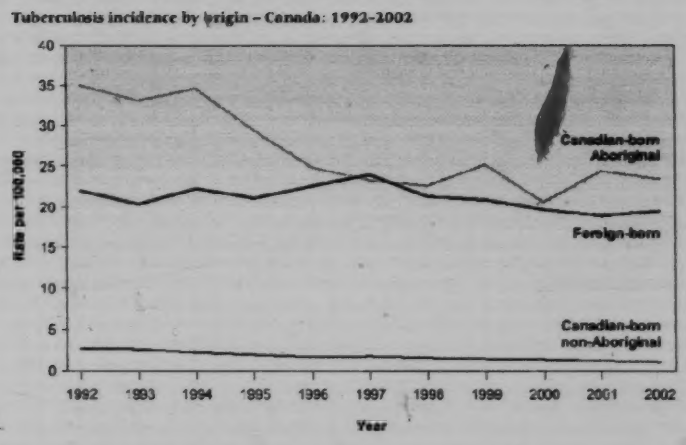


Figure 5.3: TB incidence rate by origin in Canada from 1992-2002 (PHAC).

Groups in the UK	Proportion in total population	Proportion of TB Cases	Incidence rate cases per 100,000
Non-UK born	7.5%	72%	103.3
UK-born	92.5%	28%	4.2
Total	60,111,300	8,113	14.7

Table 5.3: The UK 2005 TB data summary (HPA).

while it becomes 61.9 among immigrants.

In the United States, the proportion of TB cases for foreign-born is 21.6% in 1986, 29.8% in 1993 and 41.6% in 1998 [50, 105, 128]. The TB incidence rate for foreign-born decreased from 34.1 in 1993 to 30.1 in 1998 [128]. The total TB cases contributed by foreign-born are 4925 in 1986, 7346 in 1993 to 7591 in 1998. The TB case rate is 32.9 for foreign-born and 5.8 for US-born [28, 139].

Data in Table 5.3 is obtained from annual surveillance report of the Health Protection Agency (HPA) in UK ([63, 64, 65, 121]). The data from the UK shows a somewhat different trend from those in other developed countries. The TB incidence rate among non-UK born population is on the rise, while the incidence rate among UK born population remains relatively constant, see Figure 5.4.

Comparing the situation between the UK and Canada, we found that TB incidence among non-UK born population is increasing all the time and that of foreign-born in

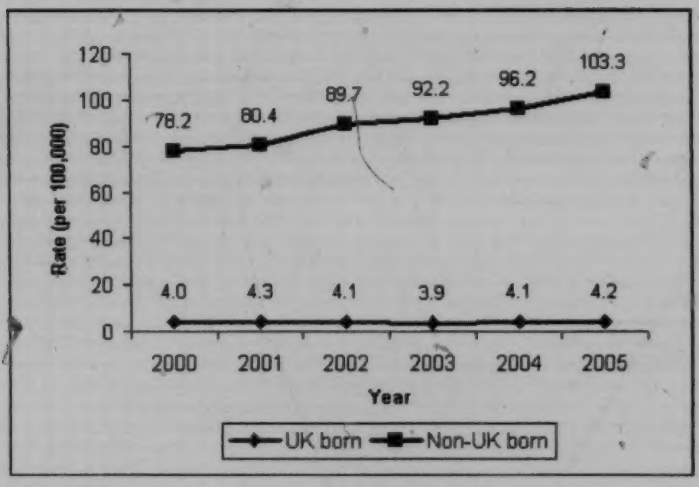


Figure 5.4: TB incidence rate for UK-born and non-UK born populations from 2000-2005 (HPA).

Canada remains relatively constant. In the mean time, TB incidence among UK-born population remains constant and that of Canadian-born population is decreasing all the time. One common point is that proportion of active TB cases contributed by the foreign-born population increases annually.

Total population of the UK is double that of Canada and the number of active TB cases in the UK is around 5-fold that of Canada. Canada has more immigrants (6.5 million, 2005) than that of the UK (4.9 million, 2005). Two countries' medical surveillance systems are similar and average life expectancy is close. Why there is a big difference on TB incidence between these two countries? What is the intrinsic dynamic mechanism which caused the difference?

It has been suggested in the UK [65] that cross-infection between non-UK born and UK-born population may explain the constant TB incidence rate in the UK-born population, while studies in Canada [108] cast doubts on the effects of such cross-infection. We propose a three-population TB model with migration and cross-infection among different groups to investigate qualitatively and quantitatively the intrinsic factors of the TB dynamics in Canada and the UK.

Over the past decade most of the 250,000 new immigrants who arrived in Canada annually are adults, and more than 80% of them were from TB-endemic countries [29].

Among the annual new immigrants, it was estimated that 40% of new immigrants are positive for tuberculin skin test [108]. This indicates that there are almost half of annual new immigrants with latent TB, some of them will develop TB quickly after entry and a fraction of them will develop TB during later time. Due to strict immigration medical checks before entry, new immigrants with active TB at arrival are rare (except for refugees [20]).

The percentage of new immigrants who develop TB after arrival is estimated in several studies. In 1998 [20], it was estimated that 8% of foreign-born TB cases reported in Canada who developed TB within the first year arrival, 18% developed active TB within 2 years and 37% within five years. Another study from Australia is shown in Figure 5.5. Since most immigrants are adults and they are infected with

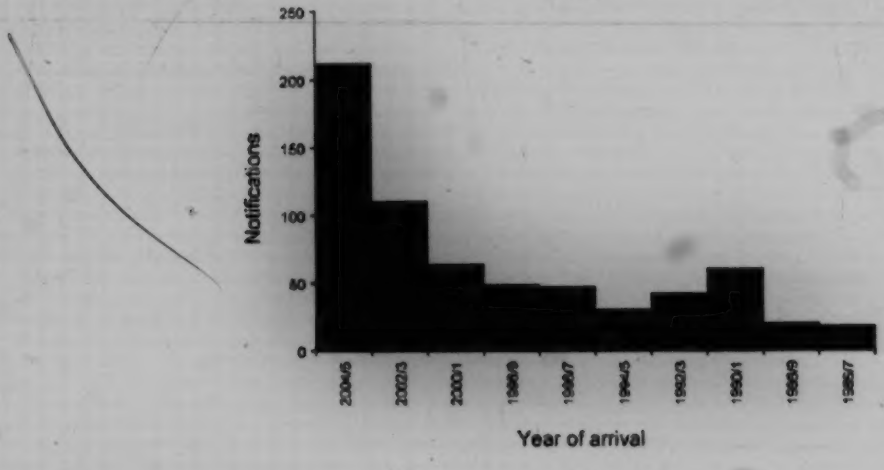


Figure 5.5: 2005 TB notification numbers of immigrants who develop TB after arrival in Australia.

latent TB before entry, there is a highest risk to develop active TB within the first few years' arrival [62, 63, 64, 79]. A more detailed comparison of probability of new immigrants who develop active TB after arrival among the UK, Canada and Australia is given in Table 5.4.

Groups classification	Non-UK born 2000-2005, the UK	Foreign-born 2002, Canada	Overseas-born 2005, Australia
within 2 years' arrival	22%	25%	23%
3 or more years prior	78%	75%	74%
Total	100%	100%	100%

Table 5.4: Percentage of latently-infected immigrants who develop TB after entry in three different studies.

5.3 A three-population model for TB

The data presented in the previous section clearly shows a common TB trend in immigration countries: steady increase in the proportion of reported TB cases contributed by the foreign-born population and a relative decline by local-born population as summarized in [41]. TB contributed by immigrants plays a critical role in the overall TB in immigration countries. Annual new immigrants with latent TB mostly from developing countries, contributed sustaining imported TB to the foreign-born population. Thus it is important to understand the impact of new immigrants with latent TB on the transmission dynamics of TB within foreign-born population in immigration countries, and to investigate effects of cross-infection between immigrants and local-born population within immigration countries.

Motivated by the TB data presented in Section 5.1 in this chapter, especially Canada and the UK, we formulate a three-population TB model to describe the transmission dynamics of TB among the populations: population in a developing country, the foreign-born population and the local-born population in a developed country with immigration policy. This transmission route also describes the global spread of TB from developing countries (high TB incidence) to developed countries (low TB incidence). Each population can be further divided into three epidemiological subclasses: susceptible (S_i), latent (exposed but not yet infectious) (E_i) and infectious (I_i), ($i = 0, 1, 2$). Here subscripts $0, 1, 2$ represent the populations in the developing country, the foreign-born population and the local-born population in the host country. Note that by foreign-born population, we mean all immigrants who are born outside of the host developed country. The next generation of foreign-born (immigrants) belongs to the local-born population (or local-born population).

The population in the developing country is relatively closed and it is reasonable to assume that TB transmission between susceptible and infectious occurs only within the population. The susceptible or infected immigrants move from the S_0, E_0 compartments in the developing country to the S_1, E_1 compartments in the foreign-born population in the host country with constant rates $\bar{\lambda}_S, \bar{\lambda}_E$, respectively. Susceptible individuals in the foreign-born population get TB infection from an infective individual not only within the foreign-born population but also get cross-infection from the local-born population [113]. Similarly, the susceptible individuals in the local-born population get TB infections not only from infective individual within population but also from the foreign-born population as well. Latently infected individuals among all three populations can develop TB within the first 2 years of infection or through a slower route by reactivation. The transfer diagram for the whole model is depicted in Figure 5.6. The top part (subscript '0') of the figure describes the TB transmission

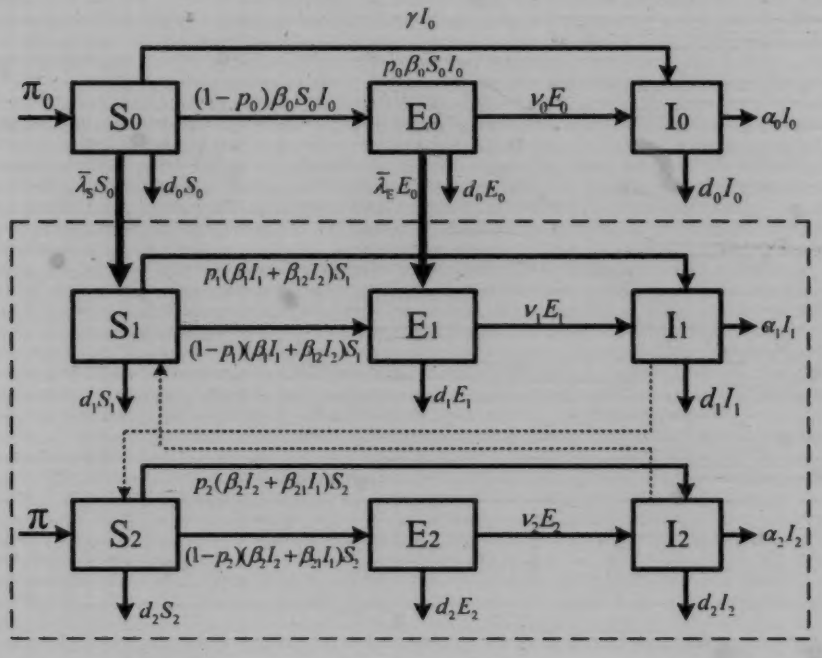


Figure 5.6: TB transmission diagram among the population from a developing country, the foreign-born and local-born populations in an immigration country. Solid lines represent population transfer or removal among compartments. Dashed lines represent cross-infection among populations. Heavy solid lines represent immigration.

π_0 :	annual new births to the population in a developing country.
β_i :	transmission coefficient between compartments S_i and I_i $(i = 0, 1, 2)$.
d_i :	removal rate in the i-th population $(i = 0, 1, 2)$.
$\bar{\lambda}_k$:	immigration rate from a developing country $(k = S, E)$.
ν_i :	slow progression rate to active TB in the i-th population $(i = 0, 1, 2)$.
p_i :	proportion of newly infected who develop TB within two years $(i = 0, 1, 2)$.
α_0 :	removal rate (TB-caused death and treatment) in a developing country.
α_k :	removal rate (TB-caused death and treatment) in the k-th population in an immigration country $(k = 1, 2)$.
π :	annual new births to local-born population in an immigration country.
β_{12} :	transmission coefficient from infective individuals (I_2) in local-born population to susceptible individuals (S_1) in foreign-born population.
β_{21} :	transmission coefficient from infective individuals (I_1) in foreign-born population to susceptible individuals (S_2) in local-born population.

Table 5.5: Parameters in the three-population TB model.

within the population in a developing country. The part inside the dashed line box describes the TB transmission within the foreign-born population (subscript '1') and the local-born population (subscript '2') within an immigration country and the cross-infection between two populations (dashed red arrows). The parameters used in the three-population TB model are described in Table 5.5.

The model is described by the following system of ordinary differential equations:

$$\begin{cases} \frac{dS_0(t)}{dt} = \pi_0 - \beta_0 S_0(t) I_0(t) - (d_0 + \lambda_S) S_0(t), \\ \frac{dE_0(t)}{dt} = (1-p_0)\beta_0 S_0(t) I_0(t) - (d_0 + \nu_0 + \lambda_E) E_0(t), \\ \frac{dI_0(t)}{dt} = p_0 \beta_0 S_0(t) I_0(t) + \nu_0 E_0(t) - (d_0 + \alpha_0) I_0(t), \\ \frac{dS_1(t)}{dt} = \lambda_S S_0(t) - \beta_1 S_1(t) I_1(t) - \beta_{12} S_1(t) I_2(t) - d_1 S_1(t), \\ \frac{dE_1(t)}{dt} = \lambda_E E_0(t) + (1-p_1)[\beta_1 S_1(t) I_1(t) + \beta_{12} S_1(t) I_2(t)] - (d_1 + \nu_1) E_1(t), \\ \frac{dI_1(t)}{dt} = p_1 \beta_1 S_1(t) I_1(t) + p_1 \beta_{12} S_1(t) I_2(t) + \nu_1 E_1(t) - (d_1 + \alpha_1) I_1(t), \\ \frac{dS_2(t)}{dt} = \pi - \beta_2 S_2(t) I_2(t) - \beta_{21} S_2(t) I_1(t) - d_2 S_2(t), \\ \frac{dE_2(t)}{dt} = (1-p_2)[\beta_2 S_2(t) I_2(t) + \beta_{21} S_2(t) I_1(t)] - (d_2 + \nu_2) E_2(t), \\ \frac{dI_2(t)}{dt} = p_2 \beta_2 S_2(t) I_2(t) + p_2 \beta_{21} S_2(t) I_1(t) + \nu_2 E_2(t) - (d_2 + \alpha_2) I_2(t). \end{cases} \tag{5.1}$$

Here $\beta_\sharp$ is transmission coefficient of the pathogen which reflects the likelihood that an infectious case will successfully transmit the infection to a susceptible individual [13]. In our model (5.1), following those in [13, 14, 117, 143], bilinear incidence forms of new infections are used. Other TB modeling used standard incidence forms [23, 27, 44, 45, 46, 112]. Also the fast and slow transmission routes to active TB, typical characters of TB progression, are incorporated in the model (5.1).

The new features in our model (5.1) are the description of global spread of TB which allows immigrants with latent TB to move from a developing country to a developed country with immigration policy, and the possible cross-infections between foreign-born population and local-born population in an immigration country.

5.4 Model reduction and strategy for model analysis

The qualitative analysis of model (5.1) with cross-infection and migration is difficult in both global behaviors and available mathematical tools. To my knowledge, no one has proved a detailed analysis for a TB with migration and cross-infection in the literature. Our strategy for the mathematical analysis of model (5.1) is as follows:

Step 1. Because no infections on population '0' are assumed to come from populations '1' and '2', we can first investigate the submodel for population '0' independent of populations '1' and '2'.

$$\begin{cases} \dfrac{dS_0(t)}{dt} = \pi_0 - \beta_0 S_0 I_0 - (d_0 + \lambda_S) S_0, \\ \dfrac{dE_0(t)}{dt} = (1-p_0)\beta_0 S_0 I_0 - (d_0 + \nu_0 + \lambda_E) E_0, \\ \dfrac{dI_0(t)}{dt} = p_0 \beta_0 S_0 I_0 + \nu_0 E_0 - (d_0 + \alpha_0) I_0. \end{cases} \tag{5.2}$$

The global dynamics of system (5.2) are described in Section 5.5.

Step 2. From Section 5.5, we know that solutions to (5.2) converge to an equilibrium as $t \to \infty$. Using the theory of asymptotically autonomous systems [25, 131], we can replace $S_0(t)$ and $E_0(t)$ that appear in equations for populations '1' and '2' by their limits, and consider the following limiting system

$$\begin{cases} \dfrac{dS_1(t)}{dt} = \lambda_S - \beta_1 S_1 I_1 - \beta_{12} S_1 I_2 - d_1 S_1, \\ \dfrac{dE_1(t)}{dt} = \lambda_E + (1-p_1)\beta_1 S_1 I_1 + (1-p_1)\beta_{12} S_1 I_2 - (d_1 + \nu_1) E_1, \\ \dfrac{dI_1(t)}{dt} = p_1 \beta_1 S_1 I_1 + p_1 \beta_{12} S_1 I_2 + \nu_1 E_1 - (d_1 + \alpha_1) I_1, \\ \dfrac{dS_2(t)}{dt} = \pi - \beta_2 S_2 I_2 - \beta_{21} S_2 I_1 - d_2 S_2, \\ \dfrac{dE_2(t)}{dt} = (1-p_2)\beta_2 S_2 I_2 + (1-p_2)\beta_{21} S_2 I_1 - (d_2 + \nu_2) E_2, \\ \dfrac{dI_2(t)}{dt} = p_2 \beta_2 S_2 I_2 + p_2 \beta_{21} S_2 I_1 + \nu_2 E_2 - (d_2 + \alpha_2) I_2, \end{cases} \tag{5.3}$$

where $\lambda_S = \bar{\lambda}_S \lim_{t\to\infty} S_0(t)$, $\lambda_E = \bar{\lambda}_E \lim_{t\to\infty} E_0(t)$. The global dynamics of system (5.3) are described in Section 5.6.

Step 3. The global dynamics of (5.1) can be obtained from those of subsystem (5.2) and the limiting system (5.3). They are described in Section 5.7.

5.5 Dynamics of the one-population submodel

Model (5.2) is same as that in [13] and its global dynamics are given in [55]. The feasible region is

$$\Gamma = \{(S_0, E_0, I_0) \in \mathbb{R}^3_+ \mid S_0 \le \pi_0/(d_0 + \lambda_S), S_0 + E_0 + I_0 \le \pi_0/d\},$$

where $d = \min\{d_0+\bar{\lambda}_S, d_0+\nu_0+\bar{\lambda}_E, d_0+\alpha_0\}$. Model (5.2) has a disease-free equilibrium $P_0 = (\pi_0/(d_0+\bar{\lambda}_S), 0, 0)$ and a unique endemic equilibrium $P^* = (S_0^*, E_0^*, I_0^*)$ with

$$S_0^* = \frac{\pi_0}{\beta_0 I_0^* + d_0 + \bar{\lambda}_S}, \quad E_0^* = \frac{(1-p_0)\beta_0 S_0^* I_0^*}{d_0+\bar{\lambda}_E+\nu_0}, \quad I_0^* = -B/A > 0,$$

where

$$A = -\beta_0(d_0+\bar{\lambda}_E+\nu_0)(d_0+\alpha_0) < 0,$$

$$B = (p_0(d_0+\bar{\lambda}_E)+\nu_0)\beta_0\pi_0 - (d_0+\bar{\lambda}_E+\nu_0)(d_0+\alpha_0)(d_0+\bar{\lambda}_S).$$

The basic reproduction number is given in [55]

$$R_{01} = \frac{\beta_0[p_0(d_0+\bar{\lambda}_E)+\nu_0]\pi_0}{(d_0+\bar{\lambda}_S)(d_0+\bar{\lambda}_E+\nu_0)(d_0+\alpha_0)}.$$

The following result was proved in [55].

Theorem 5.1. *If $R_{01} \leq 1$, the disease-free equilibrium P_0 is globally asymptotically stable in the feasible region Γ and the disease dies out from the population. If $R_{01} > 1$, the disease-free equilibrium is unstable and the endemic equilibrium P^* is globally asymptotically stable in the interior of Γ. The disease always persists in the population.*

5.6 Dynamics of the two-population submodel

The two-population model (5.3) describes the intrinsic transmission dynamics between foreign-born and local-born populations in immigration countries. Its transfer diagram is shown in Figure 5.7. The feasible region is defined as

$$\Gamma = \{(S_1, E_1, I_1, S_2, E_2, I_2) \in \mathbb{R}_+^6 \mid S_1+E_1+I_1+S_2+E_2+I_2 \leq (\lambda_S+\lambda_E+\pi)/\bar{d}\},$$

where $d = \min\{d_1, d_2\}$.

By Theorem 5.1, if $R_{01} \leq 1$, system (5.2) has a disease-free equilibrium which implies $S_0(t) \to \pi_0/(d_0+\bar{\lambda}_S)$, $E_0(t) \to 0$. Setting $\lambda_S = \bar{\lambda}_S\pi_0/(d_0+\bar{\lambda}_S), \lambda_E = 0$, system (5.3)

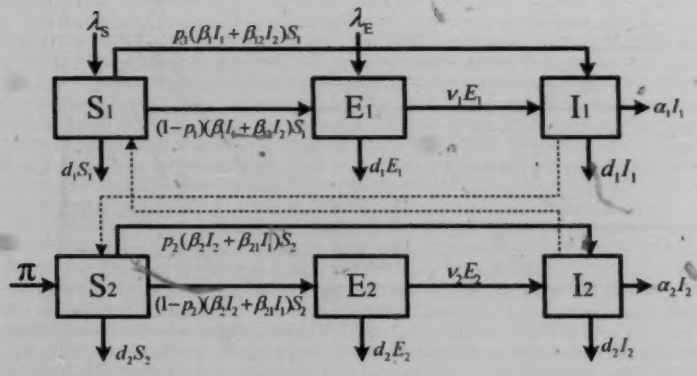


Figure 5.7: Transfer diagram for the two-population TB model (5.3).

becomes

$$\begin{cases} \dfrac{dS_1(t)}{dt} = \lambda_S - \beta_1 S_1(t) I_1(t) - \beta_{12} S_1(t) I_2(t) - d_1 S_1(t), \\ \dfrac{dE_1(t)}{dt} = (1-p_1)\beta_1 S_1(t) I_1(t) + (1-p_1)\beta_{12} S_1(t) I_2(t) - (d_1+\nu_1) E_1(t), \\ \dfrac{dI_1(t)}{dt} = p_1\beta_1 S_1(t) I_1(t) + p_1\beta_{12} S_1(t) I_2(t) + \nu_1 E_1(t) - (d_1+\alpha_1) I_1(t), \\ \dfrac{dS_2(t)}{dt} = \pi - \beta_2 S_2(t) I_2(t) - \beta_{21} S_2(t) I_1(t) - d_2 S_2(t), \\ \dfrac{dE_2(t)}{dt} = (1-p_2)\beta_2 S_2(t) I_2(t) + (1-p_2)\beta_{21} S_2(t) I_1(t) - (d_2+\nu_2) E_2(t), \\ \dfrac{dI_2(t)}{dt} = p_2\beta_2 S_2(t) I_2(t) + p_2\beta_{21} S_2(t) I_1(t) + \nu_2 E_2(t) - (d_2+\alpha_2) I_2(t). \end{cases} \tag{5.4}$$

Model (5.4) has a disease-free equilibrium $P_0 = (S_1^+, 0, 0, S_2^+, 0, 0)$ where $S_1^+ = \lambda_S/d_1$, $S_2^+ = \pi/d_2$, and a basic reproduction number

$$R_{02} = \rho(FV^{-1}), \tag{5.5}$$

where ρ denotes the spectral radius of matrix

$$FV^{-1} = \begin{bmatrix} \dfrac{p_1\beta_1 S_1^+}{d_1+\alpha_1} & \dfrac{\nu_1 p_1\beta_1 S_1^+}{(d_1+\alpha_1)(d_1+\nu_1)} & \dfrac{p_1\beta_{12} S_1^+}{d_2+\alpha_2} & \dfrac{\nu_2 p_1\beta_{12} S_1^+}{(d_2+\alpha_2)(d_2+\nu_2)} \\ \dfrac{(1-p_1)\beta_1 S_1^+}{d_1+\alpha_1} & \dfrac{\nu_1(1-p_1)\beta_1 S_1^+}{(d_1+\alpha_1)(d_1+\nu_1)} & \dfrac{(1-p_1)\beta_{12} S_1^+}{d_2+\alpha_2} & \dfrac{\nu_2(1-p_1)\beta_{12} S_1^+}{(d_2+\alpha_2)(d_2+\nu_2)} \\ \dfrac{p_2\beta_{21} S_2^+}{d_1+\alpha_1} & \dfrac{\nu_1 p_2\beta_{21} S_2^+}{(d_1+\alpha_1)(d_1+\nu_1)} & \dfrac{p_2\beta_2 S_2^+}{d_2+\alpha_2} & \dfrac{\nu_2 p_2\beta_2 S_2^+}{(d_2+\alpha_2)(d_2+\nu_2)} \\ \dfrac{(1-p_2)\beta_{21} S_2^+}{d_1+\alpha_1} & \dfrac{\nu_1(1-p_2)\beta_{21} S_2^+}{(d_1+\alpha_1)(d_1+\nu_1)} & \dfrac{(1-p_2)\beta_2 S_2^+}{d_2+\alpha_2} & \dfrac{\nu_2(1-p_2)\beta_2 S_2^+}{(d_2+\alpha_2)(d_2+\nu_2)} \end{bmatrix}.$$

Derivation of matrix FV^{-1} uses the method of next generation matrix (see [135]).

If $R_{02} \leq 1$, disease-free equilibrium P_0 is globally asymptotically stable in the feasible region Γ. If $R_{02} > 1$, system (5.4) has a unique endemic equilibrium P^* which is globally asymptotically stable in the interior of feasible region Γ.

If $R_{01} > 1$, $S_0(t) \to S_0^*$, $E_0(t) \to E_0^*$ (as $t \to \infty$) and model (5.3) becomes the case where

$$\lambda_S = \bar{\lambda}_S S_0^* > 0, \quad \lambda_E = \bar{\lambda}_E E_0^* > 0.$$

System (5.3) has a unique endemic equilibrium which is always globally asymptotically stable in the interior of feasible region Γ. In summary, we have the following theorem for model (5.3).

Theorem 5.2. *The global dynamics of* (5.3) *can be described as follows:*

Case 1. $\lambda_E = 0$.

(1) If $R_{02} \leq 1$, system (5.3) *has a disease-free equilibrium $P_0 = (S_1^+, 0, 0, S_2^+, 0, 0)$, and P^* is globally asymptotically stable in the feasible region Γ. TB dies out from the population in the developed country.*

(2) If $R_{02} > 1$, system (5.3) *has a unique endemic equilibrium $P^* = (S_1^*, E_1^*, I_1^*, S_2^*, E_2^*, I_2^*)$, and P^* is globally asymptotically stable in the interior of feasible region Γ. TB always persists in the population of developed country.*

Case 2. $\lambda_E > 0$.

When $\lambda_E > 0$, there is no basic reproduction number or disease-free equilibrium. System (5.3) *has a unique endemic equilibrium and it is globally asymptotically stable in the interior of feasible region Γ. TB always persists in the population of developed country.*

The detailed proof of Case 2 of Theorem 5.2 is given in Appendix A.

5.7 Global dynamics of the full three-population model

Now we go back to study global dynamics of the full model (5.1). According to Section 5.5, if $R_{01} \leq 1$, system (5.2) has a disease-free equilibrium and $S_0(t) \to$

$\pi_0/(d_0 + \bar{\lambda}_S)$, $E_0(t) \to 0$. Thus $\lambda_E = 0$, Case 1 in Theorem 5.2 holds.

If $R_{01} > 1$, $S_0(t) \to S_0^*$, $E_0(t) \to E_0^*$, $I_0(t) \to I_0^*$ (as $t \to \infty$), and model (5.3) becomes the case where

$$\lambda_S = \bar{\lambda}_S S_0^* > 0, \quad \lambda_E = \bar{\lambda}_E E_0^* > 0. \tag{5.6}$$

Case 2 in Theorem 5.2 implies system (5.3) has a globally stable endemic equilibrium

$$P^{**} = (S_1^{**}, E_1^{**}, I_1^{**}, S_2^{**}, E_2^{**}, I_2^{**}). \tag{5.7}$$

Thus for the full model (5.1), we have the following result, using the theory of asymptotically autonomous systems.

Theorem 5.3. *The global dynamics of system* (5.1) *are described as follows:*

Case 1. *If $R_{01} \leq 1$, system* (5.2) *has a disease-free equilibrium. TB dies out in the population of the developing country. $S_0(t) \to \pi_0/(d_0 + \bar{\lambda}_S)$, $E_0(t) \to 0, I_0(t) \to 0$. System* (5.3) *becomes* (5.4). *Furthermore,*

(a) *if $R_{02} \leq 1$, then solutions to system* (5.4) *satisfy*

$$(S_1(t), E_1(t), I_1(t), S_2(t), E_2(t), I_2(t)) \to (\lambda_S/d_1, 0, 0, \pi/d_2, 0, 0).$$

TB dies out in the populations of the developed country.

(b) *If $R_{02} > 1$, then solutions to system* (5.4) *satisfy*

$$(S_1(t), E_1(t), I_1(t), S_2(t), E_2(t), I_2(t)) \to (S_1^*, E_1^*, I_1^*, S_2^*, E_2^*, I_2^*).$$

TB persists in the populations of the developed country.

Case 2. *If $R_{01} > 1$, system* (5.2) *has a unique endemic equilibrium. TB persists in the population of the developing country. $S_0(t) \to S_0^*$, $E_0(t) \to E_0^*$, $I_0(t) \to I_0^*$. System* (5.1) *has a unique globally stable endemic equilibrium $(S_0^*, E_0^*, I_0^*, S_1^{**}, E_1^{**}, I_1^{**}, S_2^{**}, E_2^{**}, I_2^{**})$, where $P^{**} = (S_1^{**}, E_1^{**}, I_1^{**}, S_2^{**}, E_2^{**}, I_2^{**})$ is given in* (5.7). *TB always persists in the populations of the developed country.*

This is a direct result using Theorem 5.2, Theorem 5.1 and the theory of asymptotical autonomous system.

5.8 Summary

In this chapter, we propose a three-population TB model to describe the impact of migration from developing countries to developed countries on the TB transmission dynamics. The population in a developing country does not pose TB transmission to the population in an immigration country. But the accumulated foreign-born population in immigration countries has a direct impact on the TB incidence and the potential of cross-infection to the local-born population in immigration countries.

Due to the close transmission of TB within the population in a developing country, we focus on the TB transmission dynamics between foreign-born and local-born populations in an immigration country. According to the theory of asymptotically autonomous systems proposed by H. R. Thieme *et al* [131], we can reduces the full three-population TB model (5.1) into a one-population model (5.2) and a limiting system (5.3). The global dynamics of system (5.2) were established in [55]. For the two-population subsystem (5.3), we rigorously establish its global dynamics in Section 5.6 (Theorem 5.2). Then the dynamical behaviors of the full system (5.1) are established accordingly in Section 5.7 (Theorem 5.3). The proof of global stability of endemic equilibrium in Theorem 5.2 is given in Appendix A.

The significance of this chapter is as follows. The three-population model (5.1), describing the TB transmission dynamics of global spread from high TB incidence countries to low TB incidence countries, is proposed based on the TB trend in Canada and the UK. The global dynamics of the full TB model are established rigorously for the first time for a large endemic TB model in the literature. Our results show that when there are new immigrants with latent TB entering the developed country, the TB transmission dynamics in an immigration country have a unique endemic equilibrium and it is globally asymptotically stable. TB always persists in the developed countries.

Numerical simulations of our model will be carried out in the next chapter to investigate quantitatively the impact of immigrants on the TB incidence rate of foreign-born and effects of cross-infection on the TB incidence rate of local-born population in two case studies using realistic data from Canada and the UK.

Chapter 6. Case Studies: TB in Canada and the UK

In this chapter, based on the two-population TB model (5.3) proposed in Chapter 5, numerical simulations are carried out for different scenarios using data from Canada and the UK. The purpose of our simulations is to investigate quantitatively the impact of latently-infected new immigrants on the TB incidence rate of the host immigration countries, and the importance of cross-infection between foreign-born and local-born populations in Canada and the UK.

In the simulations, we use the following model equations

$$\begin{cases} \dfrac{dS_1(t)}{dt} = (1-q)(\lambda_S+\lambda_E) - S_1(t)[\beta_1 I_1(t) + \beta_{12} I_2(t)] - d_1 S_1(t), \\ \dfrac{dE_1(t)}{dt} = q(\lambda_S+\lambda_E) + (1-p_1)S_1(t)[\beta_1 I_1(t) + \beta_{12} I_2(t)] - (d_1+\nu_1)E_1(t), \\ \dfrac{dI_1(t)}{dt} = p_1 S_1(t)[\beta_1 I_1(t) + \beta_{12} I_2(t)] + \nu_1 E_1(t) - (d_1+\alpha_1)I_1(t), \\ \dfrac{dS_2(t)}{dt} = \pi - S_2(t)[\beta_2 I_2(t) + \beta_{21} I_1(t)] - d_2 S_2(t), \\ \dfrac{dE_2(t)}{dt} = (1-p_2)S_2(t)[\beta_2 I_2(t) + \beta_{21} I_1(t)] - (d_2+\nu_2)E_2(t), \\ \dfrac{dI_2(t)}{dt} = p_2 S_2(t)[\beta_2 I_2(t) + \beta_{21} I_1(t)] + \nu_2 E_2(t) - (d_2+\alpha_2)I_2(t), \end{cases} \tag{6.1}$$

where q denotes the fraction of total number of new immigrants $\lambda_S + \lambda_E$ with latent TB before entry to immigration countries. $\lambda_S + \lambda_E$ is estimated as the total number of annual new immigrants. Subscripts '1' and '2' denote the foreign-born population and local-born population in an immigration country, respectively. Terms β_{12}, β_{21} represent the rates of cross-infection between two populations.

Our simulations show that, if the TB incidence rate in the immigrant population is relatively low, as is the case of Canada, then the cross-infection to the local-born

population is small and negligible. However, if the dynamics are such that the TB incidence in the immigrant population is sufficiently high, as is the case of the UK, then the effect of cross-infection is obvious and can significantly impact the TB incidence rate of the local-born population. The comparison of the TB dynamics between Canada and the UK offers an important public health lesson: maintaining control of latent TB in new immigrants is important, and the TB incidence in the immigrant population is essential to control the overall TB problem in Canada. Failing this, the scenario currently in the UK may happen in Canada.

6.1 Simulations of Canada TB incidence

6.1.1 Parameter estimation from data

In the 2002 census [21], total immigrants in Canada is 5,639,175 and total new births are 246,038 for Canadian-born population. Total active TB cases contributed by foreign-born is 1,094 in 2002 [62]. Annual average new immigrant number is 223,840, namely, $\lambda_S + \lambda_E = 223,840$ [29]. We assume that $0 \leq q \leq 50\%$ [108]. Average life expectation in Canada is 80 years [21]. Mean age of new immigrants arriving in Canada is 30 years [29]. We assume that the removal rate for Canadian-born population is $d_2 = 0.001$, the removal rate for immigrant population is $d_1 = 0.039$. The parameter values in Table 6.1 are used in the simulations of our model (6.1).

We choose the initial values for both populations as

$$[S_1^0,\ E_1^0,\ I_1^0;\ S_2^0,\ E_2^0,\ I_2^0] = [4431746,\ 1206335,\ 1094;\ 25481638,\ 388045,\ 576].$$

This corresponds to 13% of the total immigrants within Canada who have latent TB and 1.5% of total Canadian-born people who have latent TB [62], respectively.

6.1.2 Effects of imported latent TB among new immigrants

Study 1: Suppose all new immigrants to Canada are susceptible, namely $q = 0$ in model (6.1). We assume that there is no cross-infection between two populations. Then Case 1 in Theorem 5.2 applies. If the basic reproduction number R_{02} is strictly less than 1, the TB incidences of local-born and foreign-born populations experience a decline and eventually die out, see Figure 6.1.

	Immigrant Population
$\beta_1 = 1 \times 10^{-8}$	transmission rate within immigrant population in Canada.
$d_1 = 0.039$	removal rate for immigrants in Canada.
$p_1 = 5\%$	5% high-risk LTBI immigrants develop TB in 2 years.
$v_1 = 0.00027$	1.35% low-risk LTBI immigrants develop TB in 50 years.
$\alpha_1 = 0.86$	removal rate (TB-reduced death 6%+ treatment 80%.
$\lambda_S + \lambda_E$	223,840, average annual new immigrants to Canada.
	Canadian-born Population
$\beta_2 = 0.5 \times 10^{-8}$	transmission rate within local-born population in Canada.
$d_2 = 0.001$	removal rate for Canadian-born population.
$p_2 = 1\%$	1% high-risk LTBI Canadian-born develops TB in 2 years.
$v_2 = 0.0001$	0.8% low-risk LTBI Canadian-born develop TB in 80 years.
$\alpha_2 = 0.86$	removal rate (TB-reduced death 6%+ treatment 80%).
$\pi = 246,038$	average new births in Canada.
$\beta_{21} \in [0, 1 \times 10^{-8}]$	transmission rate between foreign-born and local-born.
$\beta_{12} \in [0, 0.5 \times 10^{-8}]$	transmission rate between local-born and foreign-born.
$q \in [0, 50\%]$	% of total number of annual new immigrants with LTBI.

Table 6.1: Parameter values for simulations of the two-population TB model for Canadian-born and foreign-born populations.

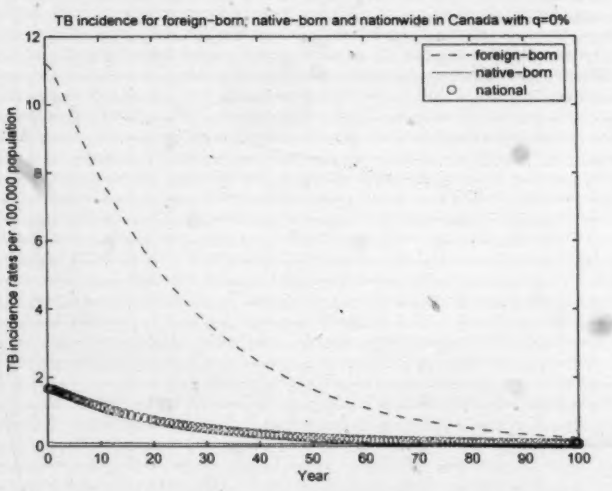


Figure 6.1: TB incidence rates in both foreign-born and Canadian-born populations decline if there is no latently-infected new immigrants to Canada.

Study 2: Suppose a percentage $q(> 0)$ of total number of all new immigrants are latently infected with TB before entry to Canada. Suppose that there is no cross-infection between Canadian-born and foreign-born populations. Then Case 2 in Theorem 5.2 applies.

Increasing the percentage q of total number of latently-infected new immigrants from 20% to 50%, we observe that the TB incidence rate in Canadian-born population always decreases while the TB incidence rate in foreign-born population increases from 6.1 (per 100,000 population) to around 15, see Figure 6.2. The national average always decreases when q increases from 20% to 50%.

6.1.3 Effects of cross-infection

Study 3: Fix $q = 40\%$, change the rate of cross-infection. We assume that cross-infection rates between Canadian-born and foreign-born populations are $\beta_{12} > 0$, $\beta_{21} > 0$. Then Case 2 in Theorem 5.2 applies. Increase β_{21} from 0 to 1×10^{-8}, the same level as β_1. We observe that TB incidence rate for foreign-born population is around 12 (per 100,000 persons per year) and TB incidence rates for Canadian-born population does not change, see Figure 6.3.

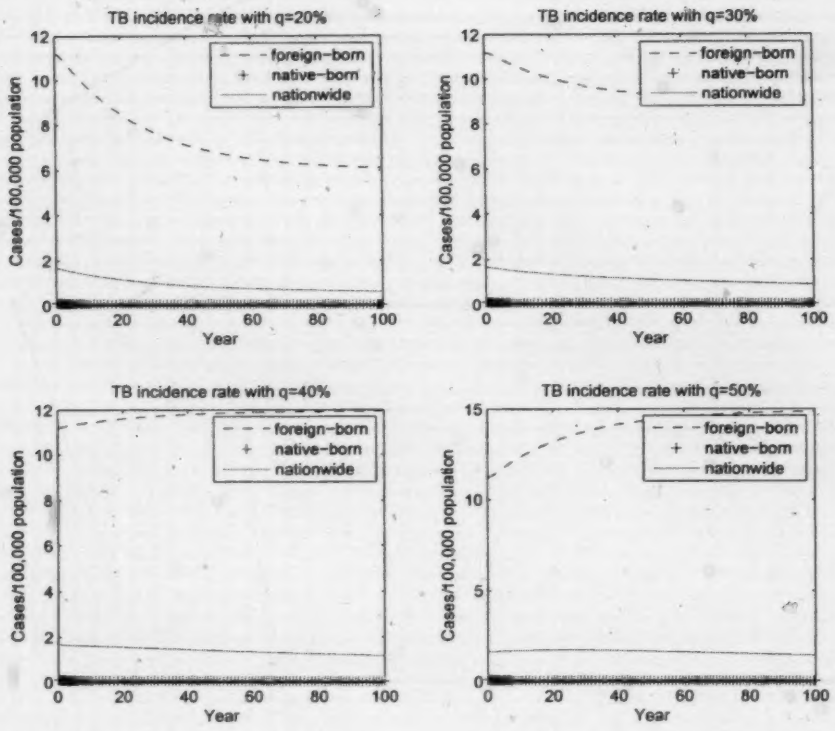


Figure 6.2: TB incidence rates for foreign-born, Canadian-born and whole country with no cross-infection.

6.1.4 Conclusions

Our simulations show that latently-infected new immigrants have a big impact on the TB incidence of foreign-born population in Canada, while they have little impact on the TB incidence of the Canadian-born population due to cross-infection.

This seems to suggest that TB is only a problem for the immigrant population, and the cross-infection to the Canadian-born population can be ignored. However, we will see a very different picture in the simulation for the UK.

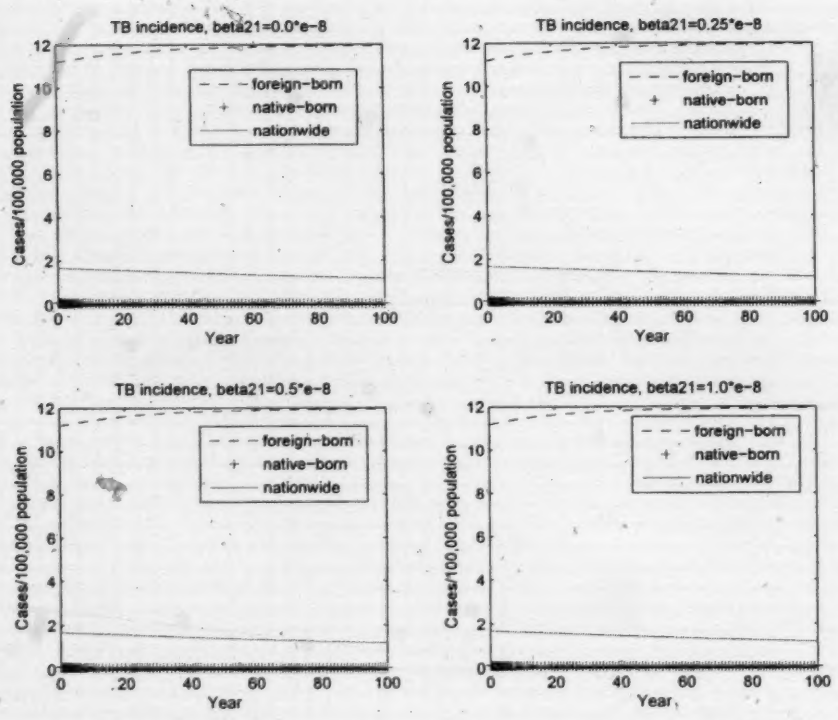


Figure 6.3: TB incidence rates for foreign-born, Canadian-born and whole country with cross-infection.

6.2 Simulation of the UK TB incidence

6.2.1 Parameter estimation from data

The average life expectation in the UK is 79 years [133]. Mean age of new immigrants is around 30 years. We assume the removal rates for non-UK born, UK-born populations are $d_1 = 0.02$, $d_2 = 0.01266$, respectively. In the 2001 census, total immigrants in the UK is 4,301,230 [39] and total new birth to UK-born population is 594,634 [133]. Total active TB cases in 2001 is 5,500 [64]. Annual average number of new immigrants is estimated to be 220,000 [39]. The parameter values in Table 6.2 are used in the simulations of our models.

	Non-UK born population
$\beta_1 = 8 \times 10^{-8}$	transmission rate within non-UK born population UK.
$d_1 = 0.02041$	removal rate for non-UK born population.
$p_1 = 0.05$	5% high-risk LTBI immigrants develop TB in 2 years.
$v_1 = 0.0021$	8.4% low-risk LTBI immigrants develop TB in next 40 years.
$\alpha_1 = 0.86$	removal rate (TB-reduced death 6%+ treatment 80%).
$\lambda_S + \lambda_E$	220,000, estimated annual new immigrants to the UK.
	UK-born population
$\beta_2 = 7 \times 10^{-8}$	transmission rate within UK-born population.
$d_2 = 0.0141$	removal rate for UK-born population.
$p_2 = 0.03$	3% high-risk LTBI UK-born develop TB in the first 2 years.
$v_2 = 0.00125$	10% low-risk LTBI UK-born develop TB in future 80 years.
$\alpha_2 = 0.86$	removal rate (TB-reduced death 6%+ treatment 80%).
$\pi = 594,634$	average new births in UK.
$\beta_{21} \in [0, 2 \times 10^{-8}]$	transmission rate between non-UK born and UK-born.
$\beta_{12} \in [0, 1 \times 10^{-8}]$	transmission rate between UK-born and non-UK born.
$q \in [0, 50\%]$	% of total number of annual new immigrants with LTBI.

Table 6.2: Parameter values for simulations of the two-population TB model for UK-born and non-UK born populations.

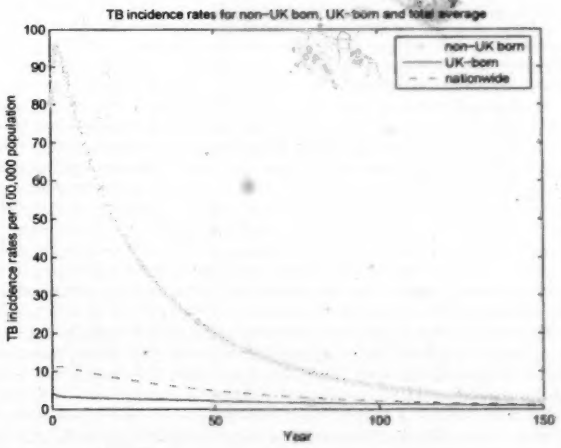


Figure 6.4: TB incidence rates for both UK-born and non-UK born populations decline if there is no latently-infected immigrants to the UK.

We choose the initial values for both populations as

$$[S_1^0,\ E_1^0,\ I_1^0;\ S_2^0,\ E_2^0,\ I_2^0] = [2362053,\ 1935727,\ 3450;\ 48195679,\ 983626,\ 2050].$$

This data indicates that 45% of the total non-UK born population have latent TB and 2% of total UK-born population have latent TB, respectively [64].

6.2.2 Effects of latent TB among new immigrants

Study 1: Suppose all new immigrants to UK are susceptible, namely, assume $q = 0$ in model (6.1). We assume that there is no cross-infection between non-UK born and UK-born populations. Then Case 1 in Theorem 5.2 applies. Thus if the basic reproduction number R_{02} is strictly less than 1, TB incidence in the non-UK born population, UK-born population and whole country have a decline trend, see Figure 6.4.

Study 2: Suppose a percentage $q(> 0)$ of total number of all new immigrants are latently infected with TB before entry to the UK. Suppose that there is no cross-infection between two populations. Then Case 2 in Theorem 5.2 applies. Increasing the percentage q from 20% to 50%, we observe that TB incidence of UK-born population

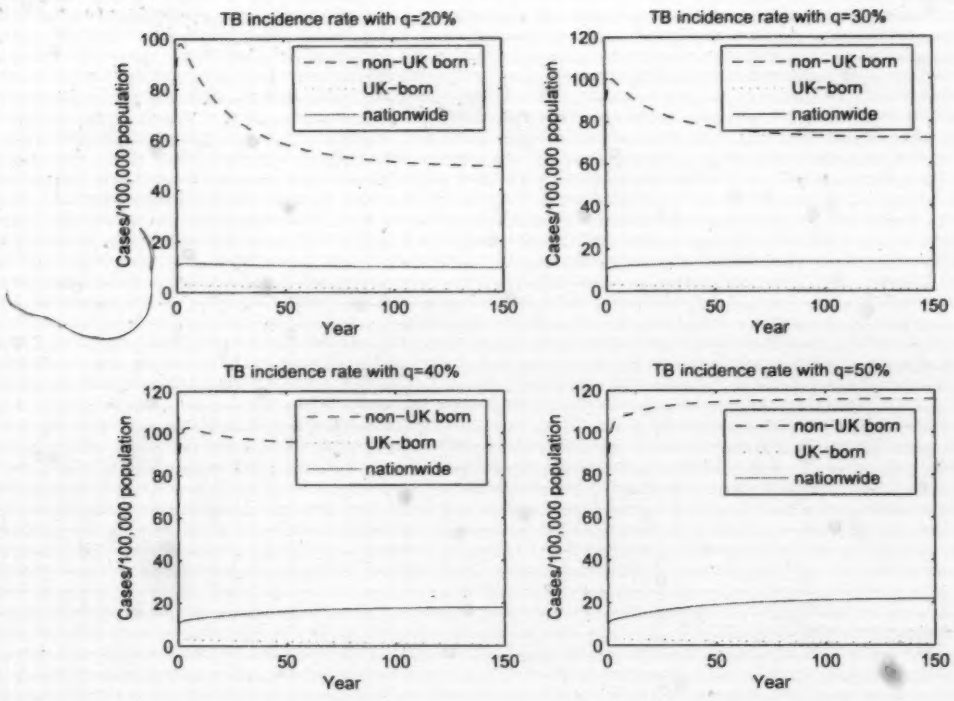


Figure 6.5: TB incidence rates for non-UK born, UK-born and whole country with increasing percentage of latently-infected new immigrants to the UK.

always decreases while the TB incidence rate of foreign-born population increases from 30 (per 100,000 persons per year) to 116 and becomes constant in a high level after a long time, see Figure 6.5. The TB incidence for national average increases from 10 to 21 when q increases from 20% to 50%.

6.2.3 Effects of cross-infection

Study 3: Fix $q = 30\%$, change the rate of cross-infection.

Case 1: If $\beta_{12} = 0$, namely, one way cross-infection rate between two populations is zero, increasing β_{21} from 0 to 3×10^{-8}, the TB incidence rate for UK-born changes gradually, first declining then increasing, see Figure 6.6.

Case 2: If $\beta_{21} = 0$, namely, one way cross-infection rate between two populations

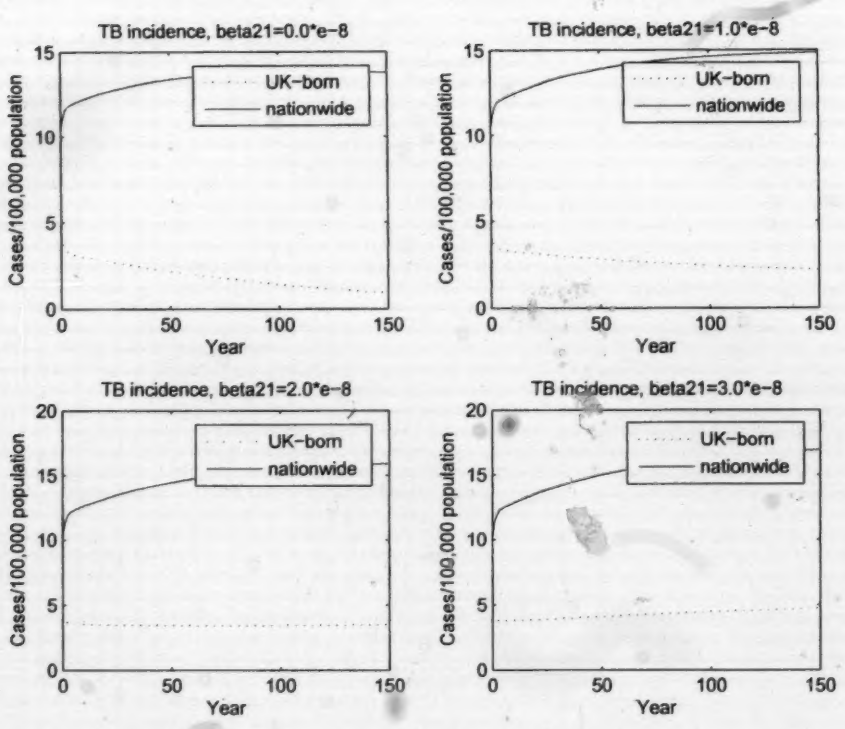


Figure 6.6: TB incidence rates for UK-born and whole country with cross-infection.

is zero, the situation is different. Increasing β_{12} from 0 to 3×10^{-8}, the TB incidence rate for UK-born population is always decreasing, see Figure 6.7.

6.2.4 Conclusions

The simulations done for two populations in the UK show that the rate of cross-infection between non-UK born and UK-born populations is evident from Figure 6.6. Also the cross-infection rate β_{21} has a bigger impact than β_{12}, indicating that infections mainly occur in one way, from the non-UK born to the UK-born. When the TB incidence for non-UK born is sufficiently high (100 per 100,000 persons per year), the cross-infection could be an important factor for the TB incidence of UK-born and national average.

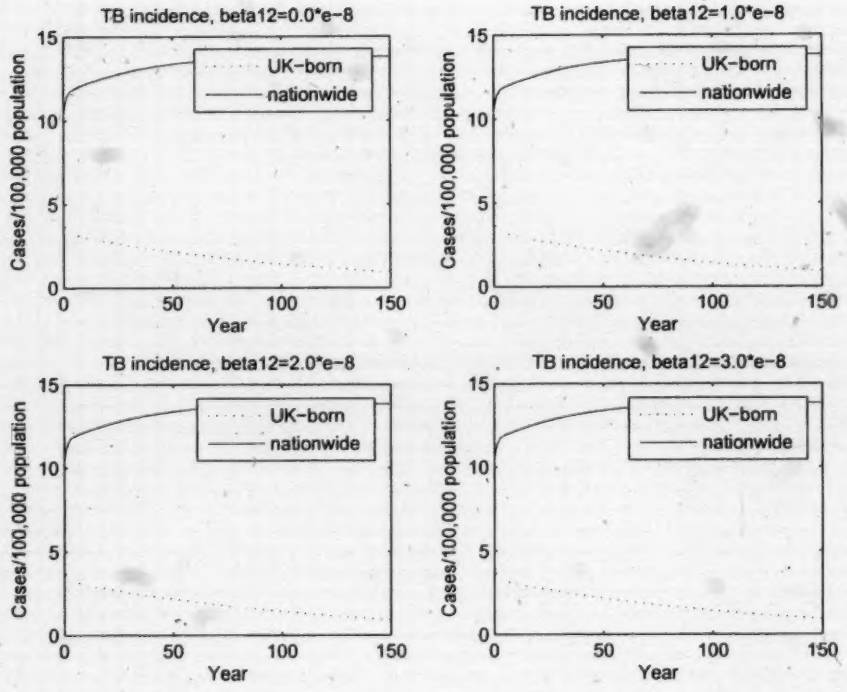


Figure 6.7: TB incidence rates for UK-born and whole country with cross-infection.

6.3 Comparison between Canada and the UK trends

Simulations of the two-population TB model describe quantitatively the TB transmission dynamics between foreign-born and local-born populations using the data from Canada and the UK.

By comparing the different TB trends in Canada and the UK, our simulations establish that cross-infection from foreign-born population to local-born population plays a key role in the TB incidence of local-born population: when the TB incidence of immigrant population is relatively low, as is the case of Canada, TB incidence in local-born population may maintain its declining trend; when the TB incidence in the immigrant population is sufficiently high, as is the case of the UK, the TB incidence in the local-born population can remain of a constant level, or even be on the rise. This confirms an earlier hypothesis given in a UK government study [64].

As an implication for Canadian public health, it is important to maintain a strict medical screening of TB for all new immigrants. Failing this, more imported latent TB cases can cause a rise in TB incidence among Canadian-born population, a case of UK scenario.

6.4 Summary

With the global dynamics of the two-population TB model (6.1) rigorously established in the previous chapter (Theorem 5.2), we carry out numerical simulations in this chapter to investigate the impact of new immigrants with latent TB on the TB incidence of the foreign-born population and the effects of cross-infection from the foreign-born to the local-born, using data from Canada and the UK.

Our results reveal that when the TB incidence rate of foreign-born population is low, as is the case of Canada, the effects of cross-infection are negligible. The influx of latent TB cases from new immigrants has no impact on the TB incidence rate of the local-born population. This agrees with findings in studies based on DNA fingerprinting technology in Canada [62] and Denmark [97]. When the TB incidence rate of the foreign-born population is sufficiently high, the cross-infection can not be neglected, as is the case of the UK. The impact of cross-infection on the TB incidence of local-born

population is significant. This agrees with epidemiological studies of TB in the UK [64, 63] and Spain [78].

The significance in this chapter is that we demonstrate quantitatively that TB cross-infection from foreign-born to local-born populations could happen under the condition that foreign-born population maintain a high TB incidence rate. Annual new immigrants with latent TB are directly responsible for the high TB incidence rate in the foreign-born population. If the proportion of new immigrants with latent TB is high, TB incidence rate in the foreign-born population can be very high and this can lead to significant cross-infection to the local-born population.

Through two epidemiologically distinct case studies in Canada and the UK, we arrived at the following conclusion: maintaining strict screening of new immigrants for active and latent TB can substantially lower the TB incidence rate in the foreign-born population in immigration countries, which in turn reduces the risk of cross-infection of TB from foreign-born to local-born populations. Failing this will not only allow the TB incidence among the foreign-born to creep up, but also change the TB trend among the local-born, as we have observed in the UK data. However, a more fundamental long-term solution to control TB in immigration countries may be to increase our efforts for controlling TB in developing countries [107].

Chapter 7. Importance of Early and Late Latency

The proportion of active TB cases contributed by foreign-born population has an increasing trend in most developed countries. To investigate the impact of latent TB cases among new immigrants on TB incidence of foreign-born population in immigration countries, we propose a four-dimensional TB model with early and late stage latent TB infection (LTBI). The purpose of the investigation is to compare the difference contributed by different proportion of latently-infected new immigrants who have a high or low risk to develop active TB after arrival.

In Section 7.1, we present the model formulation. In Section 7.2, we establish the global dynamics of the model. The proof of the global stability of the endemic equilibrium is given in Appendix B in detail. In Section 7.3, numerical simulations are carried out for different epidemiological scenarios using data from Canada.

Our simulations show that early latent TB has a bigger impact than late latent TB on incidence rate of immigrant population in developed countries. More specifically, early latent TB drives the TB incidence up quickly with a small change of percentage, while late latent TB drives TB incidence up slowly even with a big increase on percentage. Within a short period of time, controlling early LTBI can have a bigger effect than controlling late LTBI. These studies have potential benefits for policy-makers and public health authorities in developed countries with immigration policy.

7.1 A TB model with early and late latency

As presented in Chapter 5 and Chapter 6, most immigration countries experienced increasing percentage of active TB cases contributed by foreign-born population. Though strict immigration medical checks are carried out in several countries like

Canada and the UK, a sharp proportion of annual new immigrants were screened to be latently infected, indicating the infection before entry. Thus a reasonable assumption is that a proportion of annual new immigrants are latently infected but a small percentage of them are in the highest risk to develop TB after arrival.

The model incorporates fast and slow route to TB, early and late stage LTBI [143]. New feature of our model is that new immigrants have a different percentage of high or low risk to develop TB within the first two years after arrival. Using a compartmental approach, the total foreign-born population within a immigration country can be partitioned into four compartments: susceptible individuals (X), early latent stage (E) and late latent stage (L) individuals, and individuals with active TB (T). Only individuals in compartment T are infectious, and new infections result from contacts between a susceptible and an infectious individual within the immigrant population, with an incidence rate $\beta X(t)T(t)$. Here $X(t), E(t), L(t)$, and $T(t)$ denote the number of persons in the four corresponding compartments at time t. Once infected, individuals have to progress through the early latent stage with an average rate ω within the first two years. A fraction p, $0 < p \leq 1$, of these individuals progress directly to the active TB stage, and the remaining $1-p$ fraction progresses to the late latent stage. Once there, the rate of slow progression to active TB due to reactivation is at a lower rate ν. The inputs to the susceptible S, early latent stage E and late latent stage L compartments are $(1-q_1-q_2)\pi$, $q_1\pi$ and $q_2\pi$, respectively. Here π is average number of annual new immigrants and q_1, q_2 are percentages of new immigrants who are in early latent (high risk) or late latent stages (low risk) to develop TB. Due to strict immigration policies of immigration countries, we assume that there are no new immigrants with active TB before entry. The removal rates for the four compartments X, E, L, T are d_X, d_E, d_L, d_T, respectively. α is the removal rate due to TB-caused death and treatment. The dynamical transfer among the four compartments is depicted in Figure 7.1. Here all parameters are assumed to be nonnegative. The model is described by the following ODE system:

$$\begin{cases} X' = (1-q_1-q_2)\pi - \beta XT - d_X X, \\ E' = q_1\pi + \beta XT - (d_E+\omega)E, \\ L' = q_2\pi + (1-p)\omega E - (d_L+\nu)L, \\ T' = p\omega E + \nu L - (d_T+\alpha)T. \end{cases} \tag{7.1}$$

For $q_1 = q_2 = 0$, model (7.1) reduces to that in [143] and its global dynamics were

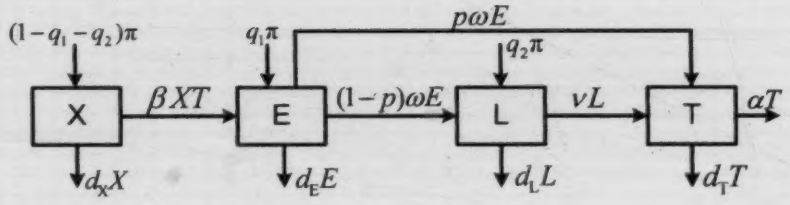


Figure 7.1: Transfer diagram for the 4-D TB model (7.1) with new immigrants in early or late latent stage.

established in [57]. If $q_1, q_2 \neq 0$, the model is called *immigration* model and its dynamical behavior is relatively simple (see [16, 104]).

7.2 Model analysis

From the first equation of (7.1), in the absence of disease, we have

$$X' \leq (1-q_1-q_2)\pi - d_X X,$$

and thus $\limsup_{t\to\infty} X(t) \leq \dfrac{(1-q_1-q_2)\pi}{d_X}$ along each solution to (7.1). The total population size in (7.1) satisfies

$$N' = (X+E+L+T)' \leq \pi - \bar{d}N - \alpha T,$$

where $\bar{d} = \min\{d_X, d_E, d_L, d_T\}$ and $N(t)$ is varying over time t and thus

$$\limsup_{t\to\infty} N(t) \leq \frac{\pi}{\bar{d}}.$$

Therefore the model (7.1) can be studied in the feasible region

$$\Gamma = \{(X,E,L,T) \in \mathbb{R}^4_+ \mid 0 \leq X \leq \frac{(1-q_1-q_2)\pi}{d_X}, 0 \leq X+E+L+T \leq \frac{\pi}{\bar{d}}\},$$

where $\mathbb{R}^4_+$ denotes the non-negative cone of $\mathbb{R}^4$ including its lower dimensional faces. It can be verified that Γ is positively invariant with respect to (7.1). We denote by $\overline{\Gamma}$ and $\overset{\circ}{\Gamma}$ the closure and the interior of Γ in $\mathbb{R}^4_+$, respectively. An equilibrium of system (7.1) satisfies the following equations

$$\begin{cases} 0 = (1-q_1-q_2)\pi - \beta XT - d_X X, \\ 0 = q_1\pi + \beta XT - (d_E+\omega)E, \\ 0 = q_2\pi + (1-p)\omega E - (d_L+\nu)L, \\ 0 = p\omega E + \nu L - (d_T+\alpha)T. \end{cases} \tag{7.2}$$

Solve X from the first equation in (7.2), we obtain

$$X = \frac{(1 - q_1 - q_2)\pi}{\beta T + d_X}. \tag{7.3}$$

Substitute the last equation into the third equation in (7.2) to cancel L term, we have

$$q_2\pi\nu + (pd_L + \nu)\omega E = (d_L + \nu)(d_T + \alpha)T. \tag{7.4}$$

Combine (7.4) with the second equation in (7.2), canceling E, we get

$$(pd_L + \nu)\omega[q_1\pi + \beta XT] + q_2\pi\nu(d_E + \omega) = (d_E + \omega)(d_L + \nu)(d_T + \alpha)T. \tag{7.5}$$

Substitute X in (7.3) into (7.5), we get

$$\begin{aligned} &q_1\pi\omega(pd_L + \nu) + q_2\pi\nu(d_E + \omega) + (pd_L + \nu)\omega\beta T\frac{(1 - q_1 - q_2)\pi}{\beta T + d_X} \\ &= (d_E + \omega)(d_L + \nu)(d_T + \alpha)T., \end{aligned} \tag{7.6}$$

Then we get a quadratic equation about T

$$f(T) \doteq AT^2 + BT + C = 0,$$

where

$$A = -\beta(d_E + \omega)(d_L + \nu)(d_T + \alpha) < 0,$$

$$C = d_X\pi[q_1\omega(pd_L + \nu) + q_2\nu(d_E + \omega)] > 0,$$

$$B = \beta(1 - q_2)\pi(pd_L + \nu) + \beta q_2\pi\nu(d_E + \omega) - d_X[(d_E + \omega)(d_L + \nu)(d_T + \alpha)].$$

The quadratic equation $f(T)$ always has a positive solution

$$T_+^* = \frac{B + \sqrt{B^2 - 4AC}}{-2A} > 0.$$

in $\mathring{\Gamma}$. Let $P^* = (X^*, E^*, L^*, T^*)$ be the endemic equilibrium for system (7.2) in $\mathring{\Gamma}$, then we have the following result.

Theorem 7.1. *Global dynamics of system* (7.1) *are described as follows:*

Case 1. $q_1 = q_2 = 0$. *([57])*

If $R_0 \leq 1$, system (7.1) always has a disease-free equilibrium which is globally asymptotically stable. TB will die out eventually in the immigrant population. If $R_0 > 1$, system (7.1) has a unique endemic equilibrium which is globally asymptotically stable in $\overset{\circ}{\Gamma}$. TB will persist in the immigrant population irrespective of any initial condition.

Case 2. *$q_1 > 0$ or $q_2 > 0$ or both.*

System (7.1) always has a unique endemic equilibrium P^* which is globally asymptotically stable in $\overset{\circ}{\Gamma}$. All solutions with positive initial conditions will be persistent and converge to the unique endemic equilibrium P^*. Any initial TB epidemics become endemic in the population.

The proof of Case 2 of Theorem 7.1 is given in Appendix B.

7.3 Case study: TB in immigrant population in Canada

Simulations of model (7.1) are carried out in this section using data from Canada. First, we investigate the impact of early or late latent stage immigrants on TB incidence in Canada. Then the effects of annual new immigrant level are considered.

7.3.1 Parameter estimation

As in Chapter 7, we assume that the removal rates for all compartments of immigrants are the same, $d_X = d_E = d_L = d_T = 0.039$. q_1 and q_2 are the percentage of total number of annual new immigrants with early latent TB ($q_1\pi$) and late latent TB ($q_2\pi$), respectively. We always assume that $q_1 < q_2$. Table 7.1 lists the parameter values used in the simulations of our model (7.1).

We choose the initial value for immigrant population in Canada as

$$[X_0, E_0, L_0, T_0] = [4431746, 9784, 1196551, 1094].$$

The above data indicates that latently infected immigrants constitute 21.4% of total immigrant population within Canada.

$\beta = 1 \times 10^{-8}$	transmission rate within immigrant population in Canada.
$d_X = 0.039$	removal rate from immigrant population.
$p = 0.05$	5% high-risk LTBI immigrants develop TB in the first 2 years.
$v = 0.0002$	1% low-risk latently-infected immigrants develop TB in next 50 years.
$\omega = 0.40$	All LTBI immigrants pass through in the first 2.5 years.
$\alpha = 0.86$	removal rate (TB-reduced death 6%+ treatment 80%).
$\pi = 223,840$	average annual new immigrants to Canada.

Table 7.1: Parameter values for simulations of the 4-D TB model (7.1) with early or late latently-infected immigrants.

7.3.2 Effects of early and late latency

Study 1: Suppose all new immigrants to Canada are susceptible ($q_1 = q_2 = 0$). Then Case 1 of Theorem 7.1 applies and TB will die out in immigrant population eventually, see Figure 7.2. This situation is similar to that of local-born population in Canada presented in last chapter. With no infected importation of new immigrants, TB incidence of immigrant population experiences a steady decline.

Study 2: Suppose that all latently-infected new immigrants to Canada have a high risk to develop TB within the first two years, $q_1 > 0$, $q_2 = 0$. Then Case 2 of Theorem 7.1 applies and TB will persist in the immigrant population. Increasing q_1 from 3% to 12%, the TB incidence rate increases from 7 (per 100,000 persons) to 26.5, see Figure 7.3.

Study 3: Suppose that all latently-infected new immigrants who have a low risk to develop TB in their lifetime in Canada, $q_2 > 0$, $q_1 = 0$. Then Case 2 of Theorem 7.1 applies and TB will persist in the immigrant population. Increasing q_2 from 20% to 50%, the TB incidence rate increased from 4.3 to 11, see Figure 7.4.

Study 4: Suppose $q_1 > 0, q_2 > 0$. Then Case 2 of Theorem 7.1 applies and TB will persist in the immigrant population. We fix $q_1 = 3\%$ and increase q_2 from 20% to 50%, the TB incidence rate increases from 17.6 to 24.1, see Figure 7.5. Fix $q_2 = 30\%$ and increase q_1 from 3% to 12%, the TB incidence rate increases from 13 to 33.1, see Figure 7.6.

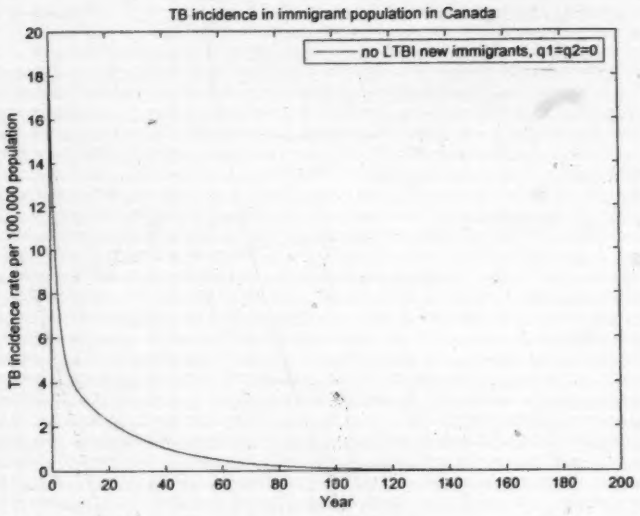


Figure 7.2: TB incidence rate in foreign-born population declines to zero without latently-infected new immigrants to Canada.

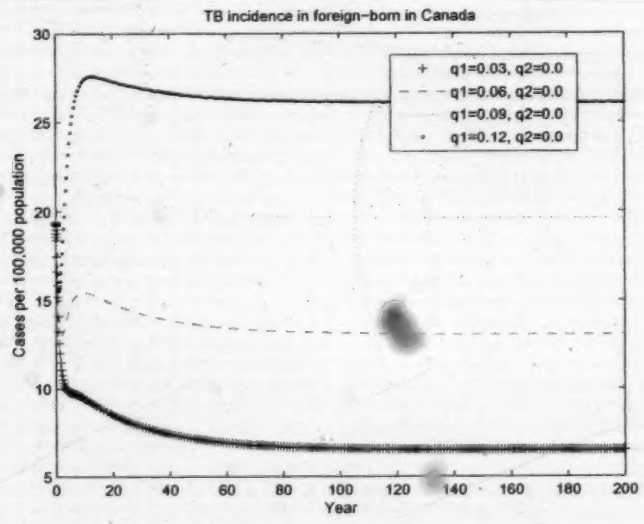


Figure 7.3: Correlation between TB incidence in foreign-born population and percentage of new immigrants in early latent stage.

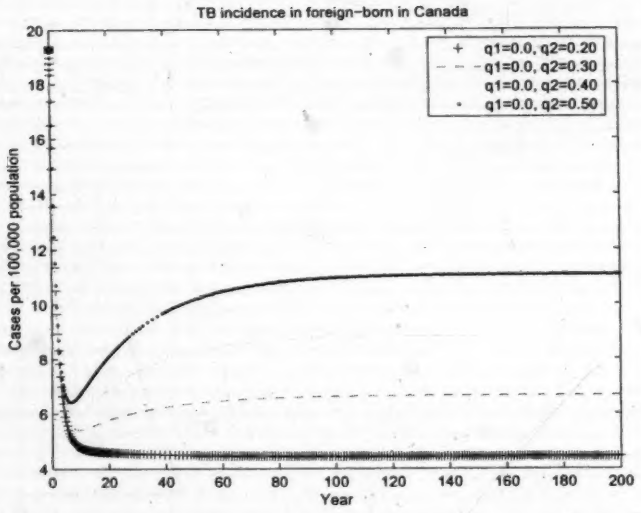


Figure 7.4: Correlation between TB incidence in foreign-born population and percentage of new immigrants in late latent stage.

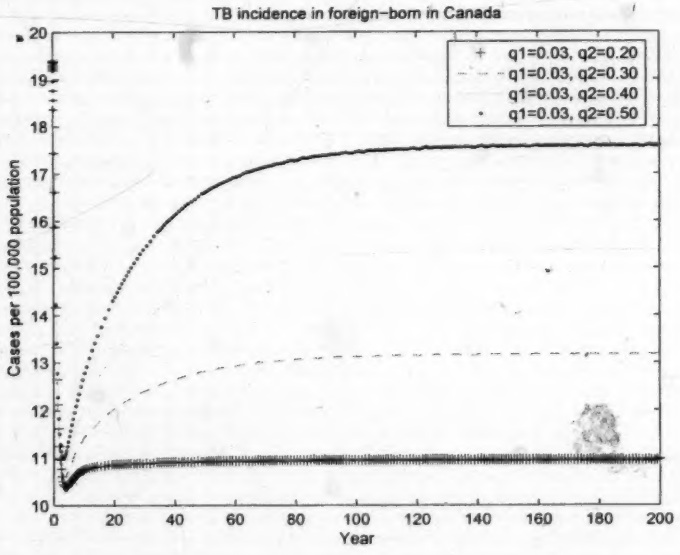


Figure 7.5: Correlation between TB incidence rate in foreign-born population and percentage of new immigrants in late latent stage.

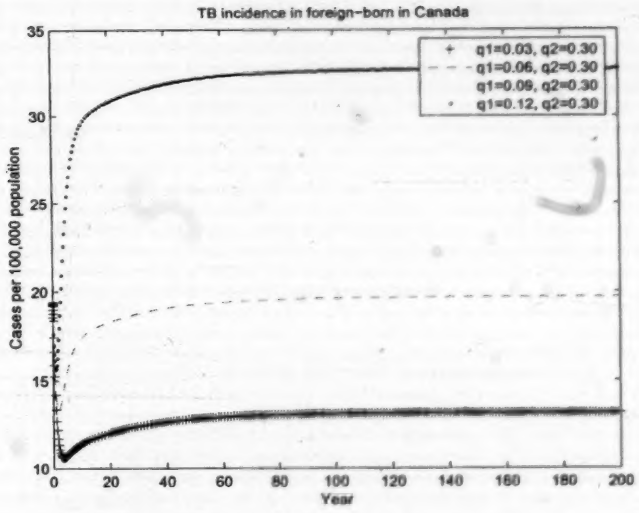


Figure 7.6: Correlation between TB incidence rate in foreign-born population and percentage of new immigrants in early latent stage.

7.3.3 Effects of annual new immigrant level

Study 5: Set q_1, q_2 in a reasonable level and increase or decrease annual level of new immigrants to Canada π. We fix $q_1 = 3\%$, $q_2 = 37\%$ and let $\pi = 111920, 223840, 447680$, respectively. Figure 7.7 shows that TB incidence rate for immigrant population changes little after a long time.

7.3.4 Conclusions

From the above figures, we observed that early LTBI immigrants have a bigger effect than late LTBI immigrants on the TB incidence in a long run. In a short term, the increase due to early LTBI immigrants is sharper than that due to late LTBI immigrants. Early LTBI is most likely to drive the TB incidence up fast while late LTBI TB increases TB incidence slowly. Doubling or halving annual new immigrant level do not change the TB incidence in the long run. But during short period, increasing annual new immigrant level sharply increases TB incidence rate. This confirms an hypothesis in an annual TB report from Health Protection Agency in the UK [64].

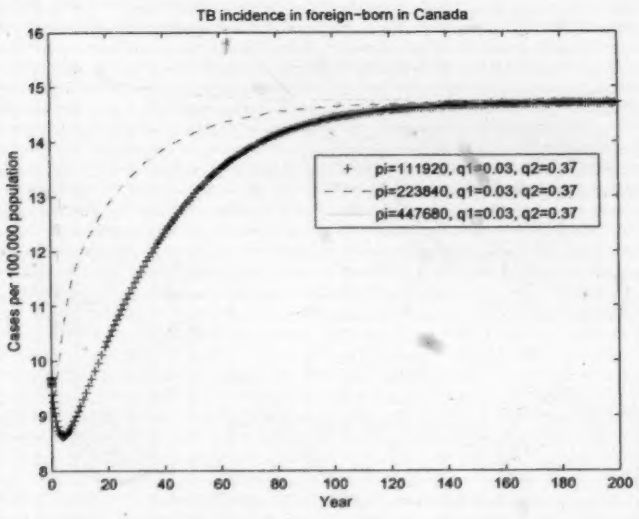


Figure 7.7: Correlation between TB incidence rate in foreign-born population and the annual new immigrant level.

7.4 Summary

In this chapter, we study a TB model with immigration to investigate the impact of early or late LTBI new immigrants on TB incidence rate of foreign-born population. We compare TB incidence rates of the foreign-born population according to different proportions of annual new immigrants with early or late stage LTBI, and the annual new immigrant levels.

Global dynamics of the model are established rigorously in Section 7.2. Our model (7.1) always has a unique endemic equilibrium P^* and it is globally asymptotically stable in the interior of feasible region Γ (Theorem 7.1). The proof of the global stability of the endemic equilibrium is given in Appendix B.

Our results show that early LTBI new immigrants drive the TB incidence fast and high. It is of a high priority to treat new immigrants with early stage LTBI. In the mean time, new immigrants with late stage LTBI would drive the TB incidence up slowly. Treatment of new immigrants with late LTBI is of a lower priority compared to those with early LTBI.

Chapter 8. Effects of Tuberculosis Immunity

It is known that acquired immunity of TB is only temporary. Recurrence of TB due to reinfection or relapse is common in some regions or countreis with high TB incidence and/or HIV epidemic [80, 88]. Most of the TB models in the literature assume permanent removals after recovery from TB. In this chapter, a TB model with partial immunity and relapses is proposed to investigate the potential impacts on TB incidence rate and the basic reproduction number in a high TB incidence setting – South Africa.

In Section 8.1, the biological background of partial immunity and relapses of TB is given and the model formulation is presented. Global dynamical behaviors of the proposed four dimensional TB model are established in Section 8.2, and a detailed proof for global stability of endemic equilibrium is given in Appendix B. In Section 8.3, numerical simulations for different scenarios of the loss of immunity and relapses of the model are carried out using realistic data from South Africa.

Our simulations show that the loss of immunity can be a very important factor for the TB transmission dynamics in countries or regions with a high TB incidence and/or HIV epidemic. Ignoring the loss of immunity in TB data analysis may substantially underestimate the basic reproduction number and the TB incidence rate.

8.1 A TB model with partial immunity and relapses

Active tuberculosis recurs in 2-7% of patients with drug-susceptible isolates treated with current standard short-course chemotherapy [32, 33]. With DNA fingerprinting

technology, cases of recurrent TB can be categorized as being due to relapse of the original infecting strain or reinfection with a new strain of M. *tuberculosis* [80]. The importance of reinfection and relapse as causes for recurrence of tuberculosis is unclear and has potential public health implications [88].

Several studies have shown that reinfection can be an increasingly common cause of recurrent tuberculosis as TB incidence rates increase. In a low-to moderate-incidence countries (i.e. TB case rates < 50 per 100,000 persons per year), studies have found the percentage of reinfection ranging from 10% in Switzerland to 33% in Spain and 16% in Italy [6, 49, 127]. In patients from low-incidence countries such as United States and Canada, the vast majority (96%) of recurrent positive cultures are due to treatment failure or relapse rather than reinfection [80].

While studies in high-burden countries (i.e. TB case rates > 200 per 100,000 persons per year), reinfection was common, ranging from 23% in Uganda [47] to 60% in a township in Cape Town, South Africa [88], with a remarkably high rate of tuberculosis ($> 1,000$ per 100,000 persons per year). Results of these studies suggest that reinfection occurs more often in high-incidence countries due to more frequent exposure to M. *tuberculosis*.

Motivated by the data presented above, we propose a TB model to investigate the impact of the loss of immunity. The total population is partitioned into four compartments: susceptible individuals (X), early latent stage (E) and late latent stage individuals (L), and individuals with active TB disease (T). The input to the susceptible compartment is π. The removal rates due to natural death or treatment for the four compartments X, E, L, T are d_X, d_E, d_L, d_T, respectively. α is the removal rate due to TB death and treatment. δ is rate of the loss of immunity and γ is the rate of relapses. The dynamical transfer among the four compartments is depicted in Figure 8.1. Here all parameters are assumed to be nonnegative. The model is described by a

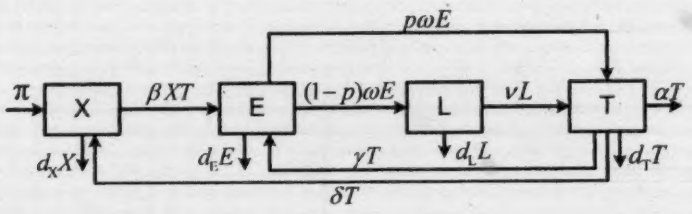


Figure 8.1: Transfer diagram for the 4-D TB model (8.1) with loss of immunity.

system of ODE

$$\begin{cases} X' = \pi - \beta XT - d_X X + \delta T, \\ E' = \beta XT + \gamma T - (d_E + \omega)E, \\ L' = (1-p)\omega E - (d_L + \nu)L, \\ T' = p\omega E + \nu L - (d_T + \alpha + \delta + \gamma)T. \end{cases} \tag{8.1}$$

If $\delta = \gamma = 0$, model (8.1) reduces to a model in [57].

8.2 Model analysis

From the first equation of (8.1), in the absence of disease, we have

$$X' \leq \pi - d_X X,$$

and thus $\limsup_{t\to\infty} X(t) \leq \frac{\pi}{d_X}$ along each solution to (8.1). The total population size in (8.1) satisfies

$$N' = (X + E + L + T)' \leq \pi - \bar{d}N - \alpha T,$$

where $\bar{d} = \min\{d_X, d_E, d_L, d_T\}$ and $N(t)$ is varying over time t and thus

$$\limsup_{t\to\infty} N(t) \leq \frac{\pi}{\bar{d}}.$$

Therefore the model can be studied in the feasible region

$$\Gamma = \{(X, E, L, T) \in \mathbb{R}^4_+ \mid 0 \leq X \leq \frac{\pi}{d_X}, 0 \leq X + E + L + T \leq \frac{\pi}{\bar{d}}\},$$

where $\mathbb{R}^4_+$ denotes the non-negative cone of $\mathbb{R}^4$ including its lower dimensional faces. It can be verified that Γ is positively invariant with respect to system (8.1). We denote by $\overline{\Gamma}$ and $\overset{\circ}{\Gamma}$ the closure and the interior of Γ in $\mathbb{R}^4_+$, respectively.

System (8.1) has a disease-free equilibrium $P_0 = (X_0, 0, 0, 0)$ with $X_0 = \pi/d_X$ and an endemic equilibrium $P^* = (X^*, E^*, L^*, T^*)$. The basic reproduction number is defined as

$$R_0 = \frac{\pi}{d_X X^*}, \tag{8.2}$$

where

$$
\begin{aligned}
X^* &= \frac{(d_L+\nu)(d_E+\omega)(d_T+\alpha+\delta+\gamma)-\gamma\omega(pd_L+\nu)}{(pd_L+\nu)\beta\omega},\\
T^* &= \frac{\pi-d_X X^*}{\beta X^*-\delta},\\
L^* &= \frac{(1-p)(d_T+\alpha+\delta+\gamma)}{pd_L+\nu}T^*,\\
E^* &= \frac{(d_L+\nu)(d_T+\alpha+\delta+\gamma)}{(pd_L+\nu)\omega}T^*.
\end{aligned}
\tag{8.3}
$$

The above argument naturally leads to the following result.

Theorem 8.1. *If $R_0 \le 1$, the disease-free equilibrium P_0 is the only equilibrium and is global asymptotically stable in $\overline{\Gamma}$. TB dies out from the population irrespective of the initial incidence. If $R_0 > 1$, a unique endemic equilibrium P^* exists in $\overset{\circ}{\Gamma}$, and is globally asymptotically stable in $\overset{\circ}{\Gamma}$. All solutions with positive initial conditions converge to P^*. Any initial TB epidemic becomes endemic in the population.*

The proof of GAS for disease-free equilibrium is standard. The proof of GAS for endemic equilibrium P^* is given in Appendix B.

Interpretation of R_0 in (8.2)

Let

$$
\begin{aligned}
h_1 &= \frac{p\omega}{d_E+\omega}+\frac{(1-p)\omega}{d_E+\omega}\cdot\frac{\nu}{d_L+\nu},\\
h_2 &= \frac{\gamma}{d_T+\alpha+\delta+\gamma},\\
\tau &= \frac{1}{d_T+\alpha+\delta+\gamma},
\end{aligned}
\tag{8.4}
$$

where h_1 is the fraction of both early latent (E) and latent period (L) individuals progressing to active TB class T. h_2 is the fraction of infectious individuals re-entering compartment E. τ is the standard infectious period. So the basic reproduction number can be rewritten as

$$R_0 = \frac{\beta\pi}{d_X}\cdot\frac{h_1}{1-h_1h_2}\tau.$$

Following [135], we can explain the second part of R_0 as follows. A fraction h_1 of individuals pass through compartment T at least once, a fraction $h_1^2h_2$ pass through at least twice, and a fraction $h_1^kh_2^{k-1}$ pass through at least k times, spending an average

of τ time units in compartment T on each pass. Thus, an individual introduced into compartment E spends, on average,

$$\begin{aligned} &\tau(h_1 + h_1^2 h_2 + \cdots + h_1^{k+1} h_2^k + \cdots) \\ &= \tau h_1 (1 + h_1 h_2 + \cdots (h_1 h_2)^k + \cdots) \\ &= \tau h_1 \frac{1}{1 - h_1 h_2} \end{aligned} \tag{8.5}$$

time units in compartment T over its expected lifetime. Multiplying right hand side in (8.5) by $\beta\pi/d_X$ gives R_0.

8.3 Case study: TB in South Africa

Due to loss of immunity, reinfection, relapse or multiple infections are possible within TB-endemic community [136], which causes the potential burden of disease prevention and control. In a high TB prevalence country like South Africa, this can be of quite importance for TB dynamics driven by HIV epidemic. In this section, the impact of the loss of immunity and relapses on basic reproduction number R_0 and TB incidence are investigated quantitatively.

8.3.1 Parameter estimation

We assume that the removal rate in each compartment equals and let $d = d_X = d_E = d_L = d_T$. Parameter estimations for vital dynamics are available from census data or annual population estimation from Statistics South Africa [126]. Parameter values in Table 8.1 are used in our simulations.

8.3.2 Impact of the loss of immunity on the basic reproduction number

From (8.2) and (8.3), we have

$$R_0 = \frac{\beta\pi}{d_X} \cdot \frac{(pd_L + \nu)\omega}{(d_L + \nu)(d_E + \omega)(d_T + \alpha + \delta + \gamma) - \gamma(pd_L + \nu)\omega}, \tag{8.6}$$

where α is the removal rate due to TB-caused death and treatment.

Parameters	definition	the value we use	reference
p	fraction of fast TB	10%	[13]
ν	reactivation rate	0.005	[13]
β	transmission rate	2×10^{-8}	[13]
ω	progression rate	0.5	[13]
α	removal rate (TB death+treatment)	$0.135 - 0.635$	WHO
δ	rate of partial immunity	0-0.50	estimate
γ	rate of relapses	0-0.50	estimate
π	recruitment rate	1,082,000	Stat SA
d	removal rate	$1/46$ year^{-1}	Stat SA
$N(0)$	initial total population	43,586,097	Stat SA
$T(0)$	initial TB cases	227,320	Stat SA

Table 8.1: Parameter values for simulations of the 4-D TB model with loss of immunity. Stat SA: Statistics South Africa.

Assume that total removal rate (except d_T) from compartment T in model (8.1) is a constant C, i.e. $\alpha + \delta + \gamma \equiv C$. We investigate the impact of the loss of immunity on the basic reproduction number and TB incidence rate.

Keeping γ fixed and increasing δ, we see from (8.6) that R_0 does not change. If we fix δ and increase γ, we see from (8.6) that R_0 increases. This shows that loss of immunity has no effects on the basic reproduction number R_0, while relapses do change R_0.

Ignoring γ may underestimate the basic reproduction number R_0. In Figure 8.2, we observe that when γ increases from 10% to 30%, the basic reproduction number R_0 increases from 2.49 to 3.27, increased by 31%. When γ increases from 30% to 50%, the basic reproduction number R_0 increases from 3.27 to 4.86, increased by 48%.

8.3.3 Effects of the loss of immunity on TB incidence

In this section, we focus on the impact of the loss of immunity on the TB incidence rate. Simulations are carried out for the effects of partial immunity and relapses, respectively.

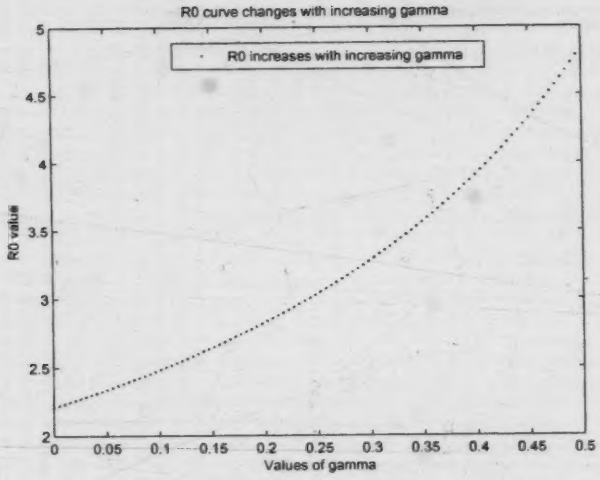


Figure 8.2: Dependence of R_0 on the rate of relapses γ.

Effects of partial immunity

Note

$$T^* = \frac{\pi - d_X X^*}{\beta X^* - \delta}, \tag{8.7}$$

where

$$X^* = \frac{(d_L + \nu)(d_E + \omega)(d_T + \alpha + \delta + \gamma) - \gamma\omega(pd_L + \nu)}{(pd_L + \nu)\beta\omega}. \tag{8.8}$$

Suppose that $\alpha + \delta + \gamma$ is a constant C, setting $\gamma = 0$, (8.8) becomes

$$X^* = \frac{(d_L + \nu)(d_E + \omega)C}{(pd_L + \nu)\beta\omega}.$$

Increasing δ, X^* doesn't change but T^* increases. In simulation shown in Figure 8.3, δ increases from 10%, 30% to 50%, TB incidence rate T^* increases from 665, 723 to 790, respectively, approximated by 9%.

Effects of relapses

Suppose that $\alpha + \gamma + \delta = C$ and let $\delta = 0$. (8.7) becomes

$$T^* = \frac{\pi - d_X X^*}{\beta X^*} = \frac{\pi}{\beta X^*} - \frac{d_X}{\beta}.$$

Increasing γ, X^* decreases thus T^* increase.

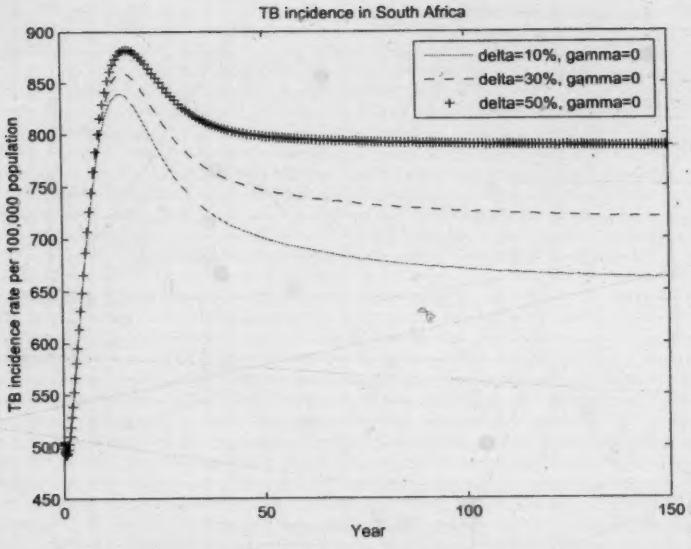


Figure 8.3: Correlation between TB incidence and the rate of partial immunity δ.

In simulation shown in Figure 8.4, we see that as γ increases from 10%, 30% to 50%, TB incidence rate increases from 670, 752 to 845, respectively, an increase of 12%.

8.3.4 Conclusions

The loss of immunity can be a very important factor for the TB dynamics [47]. Our simulations show that: R_0 does not change with the rate of loss of immunity δ. While increasing the rate of relapses γ will increases R_0. Thus ignoring the loss of immunity may underestimate R_0. Increasing both γ and δ lead to an increase of the TB incidence rate T^*. Ignoring δ and γ may underestimate the TB incidence rate.

8.4 Summary

Earlier TB models (see e.g. [27, 44]) do not consider the loss of immunity; individuals recovered from TB are assumed to be permanently removed, and will not return to the susceptible class.

In this chapter, we propose a class of TB models with partial immunity to investigate

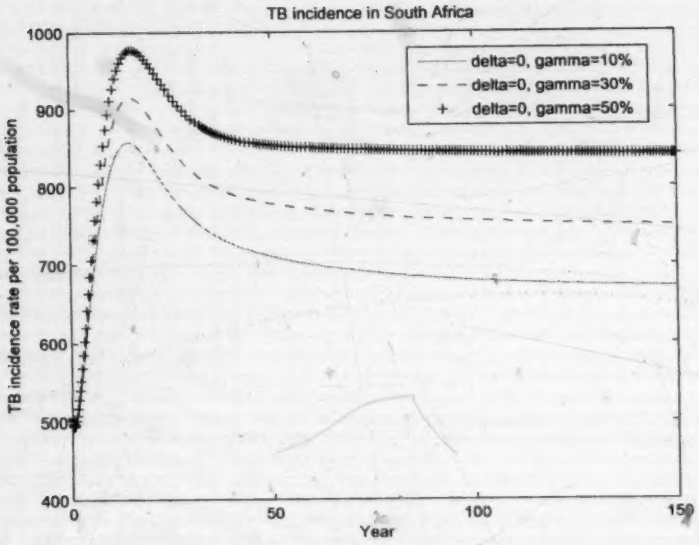


Figure 8.4: Correlation between TB incidence and the rate of relapses γ.

the potential impacts of loss of immunity on the TB incidence rate and the basic reproduction number. Our results reveal that ignoring the loss of immunity of TB may substantially underestimate the TB incidence and the basic reproduction number. The interpretation of basic reproduction number is explained following [135]. Mathematically, we established the global stability of the endemic equilibrium for this new class of models.

Appendix A. Proof of Theorem (5.2) for the two-population TB model

In the subsequent proof, we use λ_1, λ_2 instead of λ_S, λ_E as that in (5.3). We also incorporate another parameter σ into the model, which can be explained as the fraction of susceptible immigrants who visit a TB endemic country and catch TB infection before returning to the host country. Then the model (5.3) becomes

$$\begin{cases} S_1' = \lambda_1 - \beta_1 S_1 I_1 - \beta_{12} S_1 I_2 - (d_1 + \sigma) S_1, \\ E_1' = \lambda_2 + (1-p_1)\beta_1 S_1 I_1 + (1-p_1)\beta_{12} S_1 I_2 + \sigma S_1 - (d_1 + \nu_1) E_1, \\ I_1' = p_1 \beta_1 S_1 I_1 + p_1 \beta_{12} S_1 I_2 + \nu_1 E_1 - (d_1 + \alpha_1) I_1, \\ S_2' = \pi - \beta_2 S_2 I_2 - \beta_{21} S_2 I_1 - d_2 S_2, \\ E_2' = (1-p_2)\beta_2 S_2 I_2 + (1-p_2)\beta_{21} S_2 T_1 - (d_2 + \nu_2) E_2, \\ I_2' = p_2 \beta_2 S_2 I_2 + p_2 \beta_{21} S_2 I_1 + \nu_2 E_2 - (d_2 + \alpha_2) I_2. \end{cases} \tag{A.1}$$

Let the endemic equilibrium of system (A.1) denoted by $P^* = (S_1^*, E_1^*, I_1^*, S_2^*, E_2^*, I_2^*)$ whose coordinates satisfy the following equation

$$\begin{cases} \lambda_1 = \beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^* + (d_1 + \sigma) S_1^*, \\ 0 = \lambda_2 + (1-p_1)\beta_1 S_1^* I_1^* + (1-p_1)\beta_{12} S_1^* I_2^* + \sigma S_1^* - (d_1 + \nu_1) E_1^*, \\ 0 = p_1 \beta_1 S_1^* I_1^* + p_1 \beta_{12} S_1^* I_2^* + \nu_1 E_1^* - (d_1 + \alpha_1) I_1^*, \\ \pi = \beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^* + d_2 S_2^*, \\ 0 = (1-p_2)\beta_2 S_2^* I_2^* + (1-p_2)\beta_{21} S_2^* T_1^* - (d_2 + \nu_2) E_2^*, \\ 0 = p_2 \beta_2 S_2^* I_2^* + p_2 \beta_{21} S_2^* I_1^* + \nu_2 E_2^* - (d_2 + \alpha_2) I_2^*. \end{cases} \tag{A.2}$$

Combine the second and third equations in (A.2) and cancel the E_1^* term, we have

$$\nu_1 \lambda_2 + (p_1 d_1 + \nu_1)\beta_1 S_1^* I_1^* + (p_1 d_1 + \nu_1)\beta_{12} S_1^* I_2^* + \nu_1 \sigma S_1^* = (d_1 + \nu_1)(d_1 + \alpha_1) I_1^*. \tag{A.3}$$

Combine the last two equations in (A.2) and cancel the E_2^* term, we have

$$(p_2 d_2 + \nu_2)\beta_2 S_2^* I_2^* + (p_2 d_2 + \nu_2)\beta_{21} S_2^* I_1^* = (d_2 + \nu_2)(d_2 + \alpha_2) I_2^*. \tag{A.4}$$

We prove the following result, which contains Theorem 5.2 as a special case ($\sigma = 0$).

Theorem A.1. *The endemic equilibrium P^* is globally asymptotically stable in the interior of Γ.*

Proof. Set $x = (S_1, E_1, I_1, S_2, E_2, I_2) \in \Gamma \subset \mathbb{R}^+_6$. Consider a Lyapunov function V

$$\begin{aligned} V(x) &= k_1\Big[A_1\Big(S_1 - S_1^* - S_1^* \ln \frac{S_1}{S_1^*}\Big) + B_1\Big(E_1 - E_1^* - E_1^* \ln \frac{E_1}{E_1^*}\Big) \\ &\qquad + C_1\Big(I_1 - I_1^* - I_1^* \ln \frac{I_1}{I_1^*}\Big)\Big] \\ &+ k_2\Big[A_2\Big(S_2 - S_2^* - S_2^* \ln \frac{S_2}{S_2^*}\Big) + B_2\Big(E_2 - E_2^* - E_2^* \ln \frac{E_2}{E_2^*}\Big) \\ &\qquad + C_2\Big(I_2 - I_2^* - I_2^* \ln \frac{I_2}{I_2^*}\Big)\Big], \end{aligned}$$

where $x^* = P^* = (S_1^*, E_1^*, I_1^*, S_2^*, E_2^*, I_2^*)$ and

$$\begin{aligned} &k_1 = A_2\beta_{21}S_2^*I_1^*,\ A_1 = p_1d_1 + \nu_1,\ B_1 = \nu_1,\ C_1 = d_1 + \nu_1, \\ &k_2 = A_1\beta_{12}S_1^*I_2^*,\ A_2 = p_2d_2 + \nu_2,\ B_2 = \nu_2,\ C_2 = d_2 + \nu_2. \end{aligned} \tag{A.5}$$

We note that $V(x) \geq 0$, for $x \in \overset{\circ}{\Gamma}$, the interior of Γ, and $V(x) = 0 \Longleftrightarrow x = x^*$. So function V is positive definite with respect to the endemic equilibrium $x^* = P^*$. Compute the derivative of V along solutions of system (A.1), we obtain

$$\begin{aligned} \frac{dV}{dt} =& k_1\left\{A_1(1 - \frac{S_1^*}{S_1})S_1' + B_1(1 - \frac{E_1^*}{E_1})E_1' + C_1(1 - \frac{I_1^*}{I_1})I_1'\right\} \\ &+k_2\left\{A_2(1 - \frac{S_2^*}{S_2})S_2' + B_2(1 - \frac{E_2^*}{E_2})E_2' + C_2(1 - \frac{I_2^*}{I_2})I_2'\right\}. \end{aligned} \tag{A.6}$$

Using (A.1) we have

$$
\begin{aligned}
&(1-\frac{S_1^*}{S_1})S_1' \\
&= \lambda_1 - \beta_1 S_1 I_1 - \beta_{12} S_1 I_2 - (d_1+\sigma)S_1 - \lambda_1 \frac{S_1^*}{S_1} + \beta_1 S_1^* I_1 + \beta_{12} S_1^* I_2 + (d_1+\sigma)S_1^* \\
&= [\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^* + (d_1+\sigma)S_1^*] - \beta_1 S_1 I_1 - \beta_{12} S_1 I_2 - (d_1+\sigma)S_1 \\
&- [\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^* + (d_1+\sigma)S_1^*]\frac{S_1^*}{S_1} + \beta_1 S_1^* I_1 + \beta_{12} S_1^* I_2 + (d_1+\sigma)S_1^* \\
&= \left(2d_1 S_1^* - d_1 S_1 - \frac{d_1 S_1^{*2}}{S_1}\right) - \beta_1 S_1 I_1 - \beta_{12} S_1 I_2 + \beta_1 S_1^* I_1 + \beta_{12} S_1^* I_2 \\
&+ \left[2\sigma S_1^* - \sigma S_1 - \sigma \frac{S_1^{*2}}{S_1}\right] + [\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^*] - [\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^*]\frac{S_1^*}{S_1} \\
&\leq -\beta_1 S_1 I_1 - \beta_{12} S_1 I_2 + \beta_1 S_1^* I_1 + \beta_{12} S_1^* I_2 + \left[2\sigma S_1^* - \sigma S_1 - \sigma \frac{S_1^{*2}}{S_1}\right] \\
&+ [\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^*] - [\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^*]\frac{S_1^*}{S_1}.
\end{aligned}
\tag{A.7}
$$

since

$$
\left(2d_1 S_1^* - d_1 S_1 - \frac{d_1 S_1^{*2}}{S_1}\right) = d_1 S_1^* \left(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}\right) \leq 0.
$$

In the second step of the above derivation, we substituted λ_1 by the first identity of (A.2). Similarly, using (A.1), we obtain

$$
\begin{aligned}
(1-\frac{E_1^*}{E_1})E_1' &= \lambda_2 + (1-p_1)\beta_1 S_1 I_1 + (1-p_1)\beta_{12} S_1 I_2 + \sigma S_1 - (d_1+\nu_1)E_1 \\
&- \lambda_2 \frac{E_1^*}{E_1} - (1-p_1)\beta_1 S_1 I_1 \frac{E_1^*}{E_1} - (1-p_1)\beta_{12} S_1 I_2 \frac{E_1^*}{E_1} - \sigma S_1 \frac{E_1^*}{E_1} \\
&+ (d_1+\nu_1)E_1^*,
\end{aligned}
\tag{A.8}
$$

$$
\begin{aligned}
(1-\frac{I_1^*}{I_1})I_1' &= p_1\beta_1 S_1 I_1 + p_1\beta_{12} S_1 I_2 + \nu_1 E_1 - (d_1+\alpha_1)I_1 \\
&- p_1\beta_1 S_1 I_1^* - p_1\beta_{12} S_1 I_2 \frac{I_1^*}{I_1} - \nu_1 E_1 \frac{I_1^*}{I_1} + (d_1+\alpha_1)I_1^*.
\end{aligned}
\tag{A.9}
$$

Noting

$$
\left(2d_2 S_2^* - d_2 S_2 - \frac{d_2 S_2^{*2}}{S_2}\right) = d_2 S_2^* \left(2 - \frac{S_2}{S_2^*} - \frac{S_2^*}{S_2}\right) \leq 0,
$$

and substituting π by the right hand side of the fourth identity of (A.2), we have

$$\begin{aligned}
(1-\frac{S_2^*}{S_2})S_2' &= \pi - \beta_2 S_2 I_2 - \beta_{21} S_2 I_1 - d_2 S_2 - \pi\frac{S_2^*}{S_2} + \beta_2 S_2^* I_2 + \beta_{21} S_2^* I_1 + d_2 S_2^* \\
&= [\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^* + d_2 S_2^*] - \beta_2 S_2 I_2 - \beta_{21} S_2 I_1 - d_2 S_2 \\
&- [\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^* + d_2 S_2^*]\frac{S_2^*}{S_2} + \beta_2 S_2^* I_2 + \beta_{21} S_2^* I_1 + d_2 S_2^* \\
&= \left(2d_2 S_2^* - d_2 S_2 - \frac{d_2 S_2^{*2}}{S_2}\right) - \beta_2 S_2 I_2 - \beta_{21} S_2 I_1 + \beta_2 S_2^* I_2 + \beta_{21} S_2^* I_1 \\
&+ [\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^*] - [\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^*]\frac{S_2^*}{S_2} \\
&\leq -\beta_2 S_2 I_2 - \beta_{21} S_2 I_1 + \beta_2 S_2^* I_2 + \beta_{21} S_2^* I_1 \\
&+ [\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^*] - [\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^*]\frac{S_2^*}{S_2}.
\end{aligned} \tag{A.10}$$

Similarly, using (A.1), we obtain

$$\begin{aligned}
(1-\frac{E_2^*}{E_2})E_2' &= (1-p_2)\beta_2 S_2 I_2 + (1-p_2)\beta_{21} S_2 T_1 - (d_2+\nu_2)E_2 \\
&- (1-p_2)\beta_2 S_2 I_2 \frac{E_2^*}{E_2} - (1-p_2)\beta_{21} S_2 T_1 \frac{E_2^*}{E_2} + (d_2+\nu_2)E_2^*,
\end{aligned} \tag{A.11}$$

$$\begin{aligned}
(1-\frac{I_2^*}{I_2})I_2' &= p_2\beta_2 S_2 I_2 + p_2\beta_{21} S_2 I_1 + \nu_2 E_2 - (d_2+\alpha_2)I_2 - p_2\beta_2 S_2 I_2^* \\
&- p_2\beta_{21} S_2 I_1 \frac{I_2^*}{I_2} - \nu_2 E_2 \frac{I_2^*}{I_2} + (d_2+\alpha_2)I_2^*.
\end{aligned} \tag{A.12}$$

Simple calculation from (A.5) leads to the following identities:

$$\begin{aligned}
A_1 &= p_1 C_1 + (1-p_1)B_1, \\
A_2 &= p_2 C_2 + (1-p_2)B_2, \\
(d_1+\nu_1)B_1 &= \nu_1 C_1, \\
(d_2+\nu_2)B_2 &= \nu_2 C_2.
\end{aligned}$$

Substituting (A.7)-(A.12) into (B.26), we have

$$\begin{aligned}\frac{dV}{dt} \le\ & k_1\Big\{A_1\Big[(\beta_1 S_1^* I_1 + \beta_{12} S_1^* I_2) + \sigma S_1^*(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}) + (\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^*)(1 - \frac{S_1^*}{S_1})\Big] \\ & + B_1\Big[\lambda_2 + \sigma S_1 - \lambda_2 \frac{E_1^*}{E_1} - (1-p_1)\beta_1 S_1 I_1 \frac{E_1^*}{E_1} - (1-p_1)\beta_{12} S_1 I_2 \frac{E_1^*}{E_1} - \sigma S_1 \frac{E_1^*}{E_1} \\ & + (d_1 + \nu_1) E_1^*\Big] \\ & + C_1\Big[-(d_1+\alpha_1) I_1 - p_1\beta_1 S_1 I_1^* - p_1\beta_{12} S_1 I_2 \frac{I_1^*}{I_1} - \nu_1 E_1 \frac{I_1^*}{I_1} + (d_1+\alpha_1) I_1^*\Big]\Big\} \\ & + k_2\Big\{A_2\Big[(\beta_2 S_2^* I_2 + \beta_{21} S_2^* I_1) + (\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^*)(1 - \frac{S_2^*}{S_2})\Big] \\ & + B_2\Big[-(1-p_2)\beta_2 S_2 I_2 \frac{E_2^*}{E_2} - (1-p_2)\beta_{21} S_2 T_1 \frac{E_2^*}{E_2} + (d_2+\nu_2) E_2^*\Big] \\ & + C_2\Big[-(d_2+\alpha_2) I_2 - p_2\beta_2 S_2 I_2^* - p_2\beta_{21} S_2 I_1 \frac{I_2^*}{I_2} - \nu_2 E_2 \frac{I_2^*}{I_2} + (d_2+\alpha_2) I_2^*\Big]\Big\}.\end{aligned} \tag{A.13}$$

(A.13) can be rewritten as

$$\begin{aligned}\frac{dV}{dt} \le\ & \Big\{k_1 A_1(\beta_1 S_1^* I_1 + \beta_{12} S_1^* I_2) - k_1 C_1(d_1 + \alpha_1) I_1 + k_2 A_2(\beta_2 S_2^* I_2 + \beta_{21} S_2^* I_1) \\ & - k_2 C_2(d_2+\alpha_2) I_2\Big\} \\ & + \Big\{k_1 A_1(\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^*) + k_1 B_1 \lambda_2 + k_1 B_1(d_1+\nu_1) E_1^* + k_1 C_1(d_1+\alpha_1) I_1^* \\ & + 2k_1 A_1 \sigma S_1^* + k_2 A_2(\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^*) + k_2 B_2(d_2+\nu_2) E_2^* + k_2 C_2(d_2+\alpha_2) I_2^*\Big\} \\ & + \Big\{k_1 A_1\Big[-\sigma \frac{S_1^* S_1^*}{S_1} - (\beta_1 S_1^* I_1^* + \beta_{12} S_1^* I_2^*)\frac{S_1^*}{S_1})\Big] \\ & + k_1 C_1\Big[-p_1\beta_1 S_1 I_1^* - p_1\beta_{12} S_1 I_2 \frac{I_1^*}{I_1} - \nu_1 E_1 \frac{I_1^*}{I_1}\Big] \\ & + k_1 B_1\Big[-\lambda_2 \frac{E_1^*}{E_1} - (1-p_1)\beta_1 S_1 I_1 \frac{E_1^*}{E_1} - (1-p_1)\beta_{12} S_1 I_2 \frac{E_1^*}{E_1} - \sigma S_1 \frac{E_1^*}{E_1}\Big] \\ & + k_2 A_2\Big[-(\beta_2 S_2^* I_2^* + \beta_{21} S_2^* I_1^*)\frac{S_2^*}{S_2}\Big] \\ & + k_2 B_2\Big[-(1-p_2)\beta_2 S_2 I_2 \frac{E_2^*}{E_2} - (1-p_2)\beta_{21} S_2 T_1 \frac{E_2^*}{E_2}\Big] \\ & + k_2 C_2\Big[-p_2\beta_2 S_2 I_2^* - p_2\beta_{21} S_2 I_1 \frac{I_2^*}{I_2} - \nu_2 E_2 \frac{I_2^*}{I_2}\Big] - k_1 p_1 d_1 \sigma S_1\Big\} \\ \doteq\ & V_1 + V_2 + V_3.\end{aligned} \tag{A.14}$$

Now we simplify V_1. Note that V_1 in (A.14) could be rewritten as

$$\begin{aligned} V_1 &= [k_1 A_1 \beta_1 S_1^* + k_2 A_2 \beta_{21} S_2^* - k_1 C_1 (d_1 + \alpha_1)] I_1 \\ &\quad + [k_2 A_2 \beta_2 S_2^* + k_1 A_1 \beta_{12} S_1^* - k_2 C_2 (d_2 + \alpha_2)] I_2, \end{aligned} \tag{A.15}$$

and identities in (A.3) could be rewritten, according to (A.5)

$$\begin{aligned} A_1 \beta_1 S_1^* + A_1 \frac{\beta_{12} S_1^* I_2^*}{I_1^*} - C_1 (d_1 + \alpha_1) &= -B_1 \frac{\lambda_2}{I_1^*} - B_1 \frac{\sigma S_1^*}{I_1^*}, \\ A_2 \beta_2 S_2^* + A_2 \frac{\beta_{21} S_2^* I_1^*}{I_2^*} - C_2 (d_2 + \alpha_2) &= 0. \end{aligned} \tag{A.16}$$

Thus V_1 becomes

$$\begin{aligned} V_1 &= k_1 [A_1 \beta_1 S_1^* - C_1 (d_1 + \alpha_1)] I_1 + k_2 A_2 \beta_{21} S_2^* I_1 \\ &\quad + k_2 [A_2 \beta_2 S_2^* - C_2 (d_2 + \alpha_2)] I_2 + k_1 A_1 \beta_{12} S_1^* I_2 \\ &= k_1 \Big[- B_1 \frac{\lambda_2}{I_1^*} - B_1 \frac{\sigma S_1^*}{I_1^*} \Big] I_1 - k_1 A_1 \frac{\beta_{12} S_1^* I_2^*}{I_1^*} + k_2 A_2 \beta_{21} S_2^* I_1 \\ &\quad - k_2 A_2 \frac{\beta_{21} S_2^* I_1^*}{I_2^*} I_2 + k_1 A_1 \beta_{12} S_1^* I_2 \\ &= k_1 \Big[- B_1 \frac{\lambda_2}{I_1^*} - B_1 \frac{\sigma S_1^*}{I_1^*} \Big] I_1 + \Big[k_2 A_2 \beta_{21} S_2^* - k_1 A_1 \frac{\beta_{12} S_1^* I_2^*}{I_1^*} \Big] I_1 \\ &\quad + \Big[k_1 A_1 \beta_{12} S_1^* - k_2 A_2 \frac{\beta_{21} S_2^* I_1^*}{I_2^*} \Big] I_2. \end{aligned} \tag{A.17}$$

For simplicity, we denote

$$\bar{\beta}_1 \doteq \beta_1 S_1^* I_1^*, \quad \bar{\beta}_2 \doteq \beta_2 S_2^* I_2^*, \quad \bar{\beta}_{12} \doteq \beta_{12} S_1^* I_2^*, \quad \bar{\beta}_{21} \doteq \beta_{21} S_2^* I_1^*.$$

Thus V_1 becomes

$$\begin{aligned} V_1 &= k_1 \Big[- B_1 \frac{\lambda_2}{I_1^*} - B_1 \frac{\sigma S_1^*}{I_1^*} \Big] I_1 \\ &\quad + \Big[\frac{k_2 A_2 \bar{\beta}_{21} - k_1 A_1 \bar{\beta}_{12}}{I_1^*} \Big] I_1 + \Big[\frac{k_1 A_1 \bar{\beta}_{12} - k_2 A_2 \bar{\beta}_{21}}{I_2^*} \Big] I_2 \\ &= k_1 \Big[- B_1 \frac{\lambda_2}{I_1^*} - B_1 \frac{\sigma S_1^*}{I_1^*} \Big] I_1, \end{aligned} \tag{A.18}$$

since $k_1 A_1 \bar{\beta}_{12} - k_2 A_2 \bar{\beta}_{21} = 0$ from (A.5).

Next we need to simplify V_2. By (A.2) and (A.5), we have

$$\begin{aligned}
V_2 &= k_1\Big[A_1(\bar\beta_1+\bar\beta_{12})+B_1\lambda_2+B_1(d_1+\nu_1)E_1^*+C_1(d_1+\alpha_1)I_1^*+2A_1\sigma S_1^*\Big]\\
&\quad+k_2\Big[A_2(\bar\beta_2+\bar\beta_{21})+B_2(d_2+\nu_2)E_2^*+C_2(d_2+\alpha_2)I_2^*\Big]\\
&= k_1\Big[2A_1(\bar\beta_1+\bar\beta_{12})+2B_1\lambda_2+B_1\sigma S_1^*+C_1\nu_1E_1^*+2A_1\sigma S_1^*\Big]\\
&\quad+k_2\Big[2A_2(\bar\beta_2+\bar\beta_{21})+C_2\nu_2E_2^*\Big]\\
&= k_1\Big[(2A_1+(1-p_1)B_1)(\bar\beta_1+\bar\beta_{12})+3B_1\lambda_2+2(B_1+A_1)\sigma S_1^*\Big]\\
&\quad+k_2(2A_2+(1-p_2)B_2)(\bar\beta_2+\bar\beta_{21})\\
&= k_1[2p_1C_1+3(1-p_1)B_1]\bar\beta_1+3k_1B_1\lambda_2+2k_1(2\nu_1+p_1d_1)\sigma S_1^*\\
&\quad+k_2[2p_2C_2+3(1-p_2)B_2]\bar\beta_2+k_1[2p_1C_1+3(1-p_1)B_1]\bar\beta_{12}\\
&\quad+k_2[2p_2C_2+3(1-p_2)B_2]\bar\beta_{21},
\end{aligned}\tag{A.19}$$

since $A_1=p_1d_1+\nu_1=p_1C_1+(1-p_1)B_1$ and $A_2=p_2C_2+(1-p_2)B_2$.

Based on partition of unity, we define

$$\begin{aligned}
y_1&=\frac{p_1C_1}{A_1}>0,\ y_2=\frac{(1-p_1)B_1}{A_1}>0,\quad y_1+y_2=1,\\
z_1&=\frac{p_2C_2}{A_2}>0,\ z_2=\frac{(1-p_2)B_2}{A_2}>0,\quad z_1+z_2=1,\\
c_1&=\frac{p_1d_1}{A_1}>0,\ c_2=\frac{\nu_1}{A_1}>0,\quad c_1+c_2=1.
\end{aligned}\tag{A.20}$$

From (A.5), we have $k_1=A_2\bar\beta_{21}$, $k_2=A_1\bar\beta_{12}$, thus the two terms in (A.19) becomes

$$\begin{aligned}
&k_1[2p_1C_1+3(1-p_1)B_1]\bar\beta_{12}+k_2[2p_2C_2+3(1-p_2)B_2]\bar\beta_{21}\\
&=A_2\bar\beta_{21}[z_2+z_1][2p_1C_1+3(1-p_1)B_1]\bar\beta_{12}\\
&\quad+A_1\bar\beta_{12}[y_1+y_2][2p_2C_2+3(1-p_2)B_2]\bar\beta_{21}\\
&=[p_2C_2+(1-p_2)B_2][2p_1C_1+3(1-p_1)B_1]\bar\beta_{12}\bar\beta_{21}\\
&\quad+[p_1C_1+(1-p_1)B_1][2p_2C_2+3(1-p_2)B_2]\bar\beta_{21}\bar\beta_{12}\\
&=\bar\beta_{12}\bar\beta_{21}\Big[6(1-p_1)(1-p_2)B_1B_2+4p_1p_2C_1C_2+5(1-p_1)p_2B_1C_2\\
&\qquad+5(1-p_2)p_1B_2C_1\Big].
\end{aligned}\tag{A.21}$$

Substitute (A.21) into (A.19), we get

$$\begin{aligned} V_2 = {} & k_1[2p_1C_1 + 3(1-p_1)B_1]\bar{\beta}_1 + 3k_1B_1\lambda_2 + 2k_1(p_1d_1 + 2\nu_1)\sigma S_1^* \\ & + k_2[2p_2C_2 + 3(1-p_2)B_2]\bar{\beta}_2 \\ & + \bar{\beta}_{12}\bar{\beta}_{21}\Big[6(1-p_1)(1-p_2)B_1B_2 + 4p_1p_2C_1C_2 + 5(1-p_1)p_2B_1C_2 \\ & + 5(1-p_2)p_1B_2C_1\Big]. \end{aligned} \tag{A.22}$$

Using (A.20), we can combine (A.18) and V_3 and separate them into 11 groups based on partition of unity:

$$\begin{aligned} & V_3 + V_1 \\ & = k_1A_1\Big[-\sigma\frac{S_1^{*2}}{S_1} - (\bar{\beta}_1 + \bar{\beta}_{12})\frac{S_1^*}{S_1})\Big] \\ & + k_1C_1\Big[-p_1\beta_1S_1I_1^* - p_1\beta_{12}S_1I_2\frac{I_1^*}{I_1} - \nu_1E_1\frac{I_1^*}{I_1}\Big] \\ & + k_1B_1\Big[-\lambda_2\frac{E_1^*}{E_1} - (1-p_1)\beta_1S_1I_1\frac{E_1^*}{E_1} - (1-p_1)\beta_{12}S_1I_2\frac{E_1^*}{E_1} - \sigma S_1\frac{E_1^*}{E_1}\Big] \\ & + k_2A_2\Big[-(\bar{\beta}_2 + \bar{\beta}_{21})\frac{S_2^*}{S_2}\Big] + k_2B_2\Big[-(1-p_2)\beta_2S_2I_2\frac{E_2^*}{E_2} - (1-p_2)\beta_{21}S_2I_1\frac{E_2^*}{E_2}\Big] \\ & + k_2C_2\Big[-p_2\beta_2S_2I_2^* - p_2\beta_{21}S_2I_1\frac{I_2^*}{I_2} - \nu_2E_2\frac{I_2^*}{I_2}\Big] \\ & + \Big[-k_1p_1d_1\sigma S_1 - k_1B_1\frac{\lambda_2I_1}{I_1^*} - k_1B_1\frac{\sigma S_1^*I_1}{I_1^*}\Big] \\ & = k_1A_1\Big[-(c_1+c_2)\frac{\sigma S_1^{*2}}{S_1} - (y_1+y_2)\frac{\bar{\beta}_1S_1^*}{S_1} - (y_1z_1 + y_1z_2 + y_2z_1 + y_2z_2)\frac{\bar{\beta}_{12}S_1^*}{S_1}\Big] \\ & + k_1C_1\Big[-p_1\beta_1S_1I_1^* - p_1(z_1+z_2)\frac{\beta_{12}S_1I_2I_1^*}{I_1} - (a_1+a_2+a_3+a_4)\frac{\nu_1E_1I_1^*}{I_1}\Big] \\ & + k_1B_1\Big[-\frac{\lambda_2E_1^*}{E_1} - (1-p_1)\frac{\beta_1S_1I_1E_1^*}{E_1} - (1-p_1)(z_1+z_2)\frac{\beta_{12}S_1I_2E_1^*}{E_1} - \frac{\sigma S_1E_1^*}{E_1}\Big] \\ & + k_2A_2\Big[-(z_1+z_2)\frac{\bar{\beta}_2S_2^*}{S_2} - (y_1z_1 + y_1z_2 + y_2z_1 + y_2z_2)\frac{\bar{\beta}_{21}S_2^*}{S_2}\Big] \\ & + k_2B_2\Big[-(1-p_2)\frac{\beta_2S_2I_2E_2^*}{E_2} - (1-p_2)(y_1+y_2)\frac{\beta_{21}S_2I_1E_2^*}{E_2}\Big] \\ & + k_2C_2\Big[-p_2\beta_2S_2I_2^* - p_2(y_1+y_2)\frac{\beta_{21}S_2I_1I_2^*}{I_2} - (b_1+b_2)\frac{\nu_2E_2I_2^*}{I_2}\Big] \\ & + k_1\Big[-p_1d_1\sigma S_1 - k_1B_1\frac{\lambda_2I_1}{I_1^*} - k_1B_1\frac{\sigma S_1^*I_1}{I_1^*}\Big] \\ & \doteq \sum_{i=1}^{11} I_i. \end{aligned} \tag{A.23}$$

Note from the second and fifth identities in (A.2), we define parameters

$$a_1 = \frac{(1-p_1)B_1\bar{\beta}_1}{C_1B_1E_1^*},\ a_2 = \frac{B_1\lambda_2}{C_1B_1E_1^*},\ a_3 = \frac{B_1\sigma S_1^*}{C_1B_1E_1^*},\ a_4 = \frac{(1-p_1)B_1\bar{\beta}_{12}}{C_1B_1E_1^*},\ \sum_{i=1}^{4} a_i = 1,$$

and

$$b_1 = \frac{(1-p_2)B_2\bar{\beta}_2}{C_2B_2E_2^*},\ b_2 = \frac{(1-p_2)B_2\bar{\beta}_{21}}{C_2B_2E_2^*},\ b_1 + b_2 = 1.$$

Applying the inequality

$$\frac{k_1 + k_2 + \cdots + x_n}{n} \geq \sqrt[n]{k_1 \cdot k_2 \cdots x_n}, \quad (x_i \geq 0, i = 1, 2, \cdots, n),$$

and the fractions of y_i, z_i, a_i, b_i, c_i, we obtain the following group of inequalities.

$$\begin{aligned} I_1 &= k_1\left\{-y_2A_1\frac{\bar{\beta}_1S_1^*}{S_1} - B_1(1-p_1)\frac{\beta_1S_1I_1E_1^*}{E_1} - C_1a_1\frac{\nu_1E_1I_1^*}{I_1}\right\} \\ &\leq -3k_1\sqrt[3]{y_2A_1\bar{\beta}_1S_1^* \cdot B_1(1-p_1)\beta_1E_1^* \cdot C_1a_1\nu_1I_1^*} \\ &= -3k_1\sqrt[3]{\bar{\beta}_1^2 \cdot [(1-p_1)B_1]^2 \cdot a_1C_1B_1E_1^*} \\ &= -3k_1(1-p_1)B_1\bar{\beta}_1. \end{aligned} \tag{A.24}$$

$$\begin{aligned} I_2 &= k_1\left\{-y_1A_1\frac{\bar{\beta}_1S_1^*}{S_1} - C_1p_1\beta_1S_1I_1^*\right\} \\ &\leq -2k_1\sqrt{y_1A_1\bar{\beta}_1S_1^* \cdot C_1p_1\beta_1I_1^*} = -2k_1\sqrt{y_1A_1\bar{\beta}_1^2 \cdot C_1p_1} \\ &= -2k_1\sqrt{\bar{\beta}_1^2 \cdot (C_1p_1)^2} = -2k_1p_1C_1\bar{\beta}_1. \end{aligned} \tag{A.25}$$

$$\begin{aligned} I_3 &= k_2\left\{-z_2A_2\frac{\bar{\beta}_2S_2^*}{S_2} - B_2(1-p_2)\frac{\beta_2S_2I_2E_2^*}{E_2} - C_2b_1\frac{\nu_2E_2I_2^*}{I_2}\right\} \\ &\leq -3k_2\sqrt[3]{z_2A_2\bar{\beta}_2S_2^* \cdot B_2(1-p_2)\beta_2E_2^* \cdot C_2b_1\nu_2I_2^*} \\ &= -3k_2\sqrt[3]{\bar{\beta}_2^2 \cdot [B_2(1-p_2)]^2 \cdot b_1C_2B_2E_2^*} \\ &= -3k_2\sqrt[3]{\bar{\beta}_2^2 \cdot [B_2(1-p_2)]^2 \cdot (1-p_2)B_2\bar{\beta}_2} \\ &= -3k_2(1-p_2)B_2\bar{\beta}_2. \end{aligned} \tag{A.26}$$

$$\begin{aligned} I_4 &= k_2\left\{-z_1A_2\frac{\bar{\beta}_2S_2^*}{S_2} - C_2p_2\beta_2S_2I_2^*\right\} \\ &\leq -2k_2\sqrt{z_1A_2\bar{\beta}_2S_2^* \cdot C_2p_2\beta_2I_2^*} = -2k_2\sqrt{\bar{\beta}_2^2 \cdot (p_2C_2)^2} \\ &= -2k_2p_2C_2\beta_2. \end{aligned} \tag{A.27}$$

$$
\begin{aligned}
I_5 &= k_1\left\{-B_1\lambda_2\frac{E_1^*}{E_1} - B_1\frac{\lambda_2}{I_1^*}I_1 - C_1a_2\frac{\nu_1E_1I_1^*}{I_1}\right\} \\
&\leq -3k_1\sqrt[3]{B_1\lambda_2E_1^*\cdot B_1\lambda_2\cdot C_1a_2\nu_1} \\
&= -3k_1\sqrt[3]{(B_1\lambda_2)^2\cdot a_2C_1B_1E_1^*} \\
&= -3k_1\sqrt[3]{(B_1\lambda_2)^2\cdot B_1\lambda_2} = -3k_1B_1\lambda_2.
\end{aligned} \tag{A.28}
$$

$$
\begin{aligned}
I_6 &= k_1\left\{-A_1c_1\sigma\frac{S_1^{*2}}{S_1} - p_1d_1\sigma S_1\right\} \\
&\leq -2k_1\sqrt{A_1c_1\sigma S_1^{*2}\cdot p_1d_1\sigma} \\
&= -2k_1\sqrt{(\sigma S_1^*)^2\cdot(p_1d_1)^2} = -2k_1p_1d_1\sigma S_1^*.
\end{aligned} \tag{A.29}
$$

$$
\begin{aligned}
I_7 &= k_1\left\{-A_1c_2\sigma\frac{S_1^{*2}}{S_1} - B_1\sigma S_1\frac{E_1^*}{E_1} - C_1a_3\nu_1E_1\frac{I_1^*}{I_1} - B_1\frac{\sigma S_1^*}{I_1^*}I_1\right\} \\
&\leq -4k_1\sqrt[4]{A_1c_2\sigma S_1^{*2}\cdot B_1\sigma E_1^*\cdot C_1a_3\nu_1\cdot B_1\sigma S_1^*} \\
&= -4k_1\sqrt[4]{A_1c_2(\sigma S_1^*)^3\cdot(B_1)^2\cdot C_1a_3B_1E_1^*} \\
&= -4k_1\sqrt[4]{B_1(\sigma S_1^*)^3\cdot(B_1)^2\cdot B_1\sigma S_1^*} = -4k_1B_1\sigma S_1^*.
\end{aligned} \tag{A.30}
$$

$$
\begin{aligned}
I_8 &= \Big\{ - k_1y_1z_1A_1\frac{\bar\beta_{12}S_1^*}{S_1} - k_1z_1C_1p_1\frac{\beta_{12}S_1I_2I_1^*}{I_1} - k_2y_1C_2p_2\frac{\beta_{21}S_2I_1I_2^*}{I_2} \\
&\quad - k_2y_1z_1A_2\frac{\bar\beta_{21}S_2^*}{S_2}\Big\} \\
&\leq -4\sqrt[4]{k_1y_1z_1A_1\bar\beta_{12}S_1^*\cdot k_1z_1C_1p_1\beta_{12}I_1^*\cdot k_2y_1C_2p_2\beta_{21}I_2^*\cdot k_2y_1z_1A_2\bar\beta_{21}S_2^*} \\
&= -4\sqrt[4]{(k_1)^2(y_1z_1)^3A_1(\beta_{12})^2\cdot p_1C_1p_2C_2\cdot(k_2)^2A_2(\bar\beta_{21})^2} \\
&= -4\sqrt[4]{(A_2\bar\beta_{21})^2(y_1z_1)^3A_1(\bar\beta_{12})^2\cdot p_1C_1p_2C_2\cdot(A_1\bar\beta_{12})^2A_2(\bar\beta_{21})^2} \\
&= -4\sqrt[4]{(A_2)^3(y_1z_1)^3(\bar\beta_{12})^4\cdot p_1C_1p_2C_2\cdot(A_1)^3(\bar\beta_{21})^4} \\
&= -4\sqrt[4]{(A_2z_1y_1A_1)^3(\bar\beta_{21})^4(\bar\beta_{12})^4\cdot p_1C_1p_2C_2} \\
&= -4\sqrt[4]{(p_2C_2p_1C_1)^3(\bar\beta_{21})^4(\bar\beta_{12})^4\cdot p_1C_1p_2C_2} = -4p_2C_2p_1C_1\bar\beta_{21}\bar\beta_{12}.
\end{aligned} \tag{A.31}
$$

$$
\begin{aligned}
I_9 &= -k_1 y_1 z_2 A_1 \frac{\bar{\beta}_{12} S_1^*}{S_1} - k_1 z_2 C_1 p_1 \frac{\beta_{12} S_1 I_2 I_1^*}{I_1} - k_2 y_1 b_2 C_2 \nu_2 E_2 \frac{I_2^*}{I_2} \\
&\le -5\sqrt[5]{(k_1 z_2)^2 y_1 A_1 (\bar{\beta}_{12})^2 \cdot p_1 C_1 \cdot b_2 C_2 \nu_2 E_2^* \cdot (1-p_2) B_2 \cdot (k_2 y_1)^3 z_2 A_2 (\bar{\beta}_{21})^2} \\
&= -5\sqrt[5]{(k_1 z_2)^2 y_1 A_1 (\bar{\beta}_{12})^2 \cdot p_1 C_1 \cdot (1-p_2) B_2 \bar{\beta}_{21} \cdot (1-p_2) B_2 \cdot (k_2 y_1)^3 z_2 A_2 (\bar{\beta}_{21})^2} \\
&= -5\sqrt[5]{(k_1 z_2)^2 y_1 A_1 (\bar{\beta}_{12})^2 \cdot p_1 C_1 \cdot [(1-p_2) B_2]^2 \cdot (k_2 y_1)^3 z_2 A_2 (\bar{\beta}_{21})^3} \\
&= -5\sqrt[5]{(k_1)^2 (z_2)^3 A_1 (k_2)^3 (y_1)^4 A_2 (\bar{\beta}_{12})^2 \cdot p_1 C_1 \cdot [(1-p_2) B_2]^2 \cdot (\bar{\beta}_{21})^3} \\
&= -5\sqrt[5]{(A_2 \bar{\beta}_{21})^2 (z_2)^3 A_1 (A_1 \bar{\beta}_{12})^3 (y_1)^4 A_2 (\bar{\beta}_{12})^2 \cdot p_1 C_1 \cdot [(1-p_2) B_2]^2 \cdot (\bar{\beta}_{21})^3} \\
&= -5\sqrt[5]{(A_2 z_2)^3 (A_1 y_1)^4 (\bar{\beta}_{12})^5 \cdot p_1 C_1 \cdot [(1-p_2) B_2]^2 \cdot (\bar{\beta}_{21})^5} \\
&= -5\sqrt[5]{[(1-p_2) B_2]^3 (p_1 C_1)^4 (\bar{\beta}_{12})^5 \cdot p_1 C_1 \cdot [(1-p_2) B_2]^2 \cdot (\bar{\beta}_{21})^5} \\
&= -5 p_1 C_1 (1-p_2) B_2 \bar{\beta}_{12} \bar{\beta}_{21}.
\end{aligned}
\tag{A.32}
$$

$$
\begin{aligned}
I_{10} &= \Big\{ - x_1 y y_2 z_1 A_1 \frac{\bar{\beta}_{12} S_1^*}{S_1} - k_1 z_1 B_1 (1-p_1) \frac{\beta_{12} S_1 I_2 E_1^*}{E_1} - k_1 z_1 C_1 a_4 \nu_1 E_1 \frac{I_1^*}{I_1} \\
&\quad - k_2 y_2 C_2 p_2 \frac{\beta_{21} S_2 I_1 I_2^*}{I_2} - k_2 y_2 z_1 A_2 \frac{\bar{\beta}_{21} S_2^*}{S_2} \Big\} \\
&\le -5\sqrt[5]{(k_1 z_1)^3 y_2 A_1 \bar{\beta}_{12}^2 \cdot (1-p_1) B_1 \cdot a_4 C_1 B_1 E_1^* \cdot p_2 C_2 \cdot (k_2 y_2)^2 z_1 A_2 \bar{\beta}_{21}^2} \\
&= -5\sqrt[5]{(k_1)^3 (k_2)^2 (z_1)^4 (y_2)^3 A_1 A_2 \bar{\beta}_{12}^2 \bar{\beta}_{21}^2 \cdot (1-p_1) B_1 \cdot p_2 C_2 \cdot (1-p_1) B_1 \bar{\beta}_{12}} \\
&= -5\sqrt[5]{(A_2 \bar{\beta}_{21})^3 (A_1 \bar{\beta}_{12})^2 (z_1)^4 (y_2)^3 A_1 A_2 \bar{\beta}_{12}^3 \bar{\beta}_{21}^2 \cdot [(1-p_1) B_1]^2 \cdot p_2 C_2} \\
&= -5\sqrt[5]{(\bar{\beta}_{21})^5 (\bar{\beta}_{12})^5 (A_2 z_1)^4 (A_1 y_2)^3 \cdot [(1-p_1) B_1]^2 \cdot p_2 C_2} \\
&= -5 \bar{\beta}_{21} \bar{\beta}_{12} \sqrt[5]{(p_2 C_2)^4 [(1-p_1) B_1]^3 \cdot [(1-p_1) B_1]^2 \cdot p_2 C_2} \\
&= -5 p_2 C_2 (1-p_1) B_1 \bar{\beta}_{21} \bar{\beta}_{12}.
\end{aligned}
\tag{A.33}
$$

$$
\begin{aligned}
I_{11} &= -k_1y_2z_2A_1\frac{\bar{\beta}_{12}S_1^*}{S_1} - k_1z_2B_1(1-p_1)\frac{\beta_{12}S_1I_2E_1^*}{E_1} - k_1z_2C_1a_4\frac{\nu_1E_1I_1^*}{I_1} \\
&\quad - x_2y_2C_2b_2\frac{\nu_2E_2I_2^*}{I_2} - k_2y_2B_2(1-p_2)\frac{\beta_{21}S_2I_1E_2^*}{E_2} - k_2y_2z_2A_2\frac{\bar{\beta}_{21}S_2^*}{S_2} \\
&\le -6\sqrt[6]{(k_1k_2)^3(z_2y_2)^4A_1A_2(\bar{\beta}_{21}\bar{\beta}_{12})^2\cdot a_4C_1\nu_1E_1^*\cdot b_2C_2\nu_2E_2^*\cdot(1-p_1)B_1(1-p_2)B_2} \\
&= -6\sqrt[6]{(A_2A_1\bar{\beta}_{21}\bar{\beta}_{12})^3(z_2y_2)^4A_1A_2(\bar{\beta}_{21}\bar{\beta}_{12})^3\cdot[(1-p_1)B_1]^2[(1-p_2)B_2]^2} \\
&= -6\sqrt[6]{(A_2z_2A_1y_2)^4\cdot(\bar{\beta}_{21}\bar{\beta}_{12})^6\cdot[(1-p_1)B_1]^2[(1-p_2)B_2]^2} \\
&= -6\sqrt[6]{[(1-p_2)B_2(1-p_1)B_1]^4\cdot(\bar{\beta}_{21}\bar{\beta}_{12})^6\cdot[(1-p_1)B_1]^2[(1-p_2)B_2]^2} \\
&= -6(1-p_2)B_2(1-p_1)B_1\bar{\beta}_{21}\bar{\beta}_{12}.
\end{aligned}
\tag{A.34}
$$

Substitute (A.24)-(A.34) into (A.23) and combine (A.22) and (A.14), we get

$$\frac{dV}{dt} \le V_1 + V_2 + V_3 \le 0.$$

Furthermore, $\frac{dV}{dt} = 0$ if and only if $S_i = S_i^*(i = 1,2)$ and equalities hold in (A.24)-(A.34). Thus it implies

$$E_i = aE_i^*,\ \ I_i = aI_i^*,\quad i = 1,2,$$

where a is an arbitrary positive number. Substitute $S_i = S_i^*,\ E_i = aE_i^*,\ I_i = aI_i^*$ into the first equation of (A.1)

$$0 = \lambda_1 - a[\beta_1S_1^*I_1^* + \beta_{12}S_1^*I_2^*] - (d_1+\sigma)S_1^*. \tag{A.35}$$

By (A.2), we know that (A.35) holds iff $a = 1$, namely at P^*. Therefore, the only compact invariant subset of the set where $\dot{V} = 0$ is the singleton $\{P^*\}$. By the LaSalle Invariance Principle, P^* is globally stable in $\overset{\circ}{\Gamma}$. This completes the proof of Theorem 5.2.

Remark:

The above proof is complicated. A simple proof can be done using the similar procedure as later part in Appendix B.

Appendix B. Two proofs of GAS of P^* for Theorem 7.1 and Theorem 8.1

In the subsequent proof, we use notations $\pi, \lambda_1, \lambda_2$ instead of $(1-q_1-q_2)\pi$, $q_1\pi$, $q_2\pi$ as appeared in model (7.1). We also incorporate terms δT and γT of model (8.1) in our unified proof for the GAS of endemic equilibrium P^* of both models. Thus the combined model of (7.1) and (8.1) is

$$\begin{cases} X' = \pi - \beta XT - d_X X + \delta T, \\ E' = \lambda_1 + \beta XT + \gamma T - (d_E + \omega)E, \\ L' = \lambda_2 + (1-p)\omega E - (d_L + \nu)L, \\ T' = p\omega E + \nu L - (d_T + \alpha + \delta + \gamma)T. \end{cases} \tag{B.1}$$

Preliminary: Let $X = S + \delta/\beta$, the first equation in (B.1) becomes,

$$\begin{aligned} S' = X' &= \pi - \beta(S+\delta/\beta)T - d_X(S+\delta/\beta) + \delta T \\ &= (\pi - d_X\delta/\beta) - \beta ST - d_X S. \end{aligned}$$

Thus the feasible region Γ is reduced to Γ_r which is defined as

$$\Gamma_r = \left\{ (S,E,L,T) \in \mathbb{R}^4_+ \mid 0 \le S \le \frac{\pi}{d_X} - \frac{\delta}{\beta}, 0 \le S+E+L+T \le \frac{\pi+\lambda_1+\lambda_2}{d} - \frac{\delta}{\beta} \right\}$$

and endemic equilibrium P^* becomes $\tilde{P}^* = (S^*, E^*, L^*, T^*)$. Similarly

$$\begin{aligned} E' &= \lambda_1 + \beta(S+\delta/\beta)T + \gamma T - (d_E+\omega)E \\ &= \lambda_1 + \beta ST + (\delta+\gamma)T - (d_E+\omega)E. \end{aligned}$$

The other two equations don't involve with variable X, so the original system (B.1) becomes

$$\begin{cases} S' = \pi - d_X\delta/\beta - \beta ST - d_X S, \\ E' = \lambda_1 + \beta ST + (\delta+\gamma)T - (d_E+\omega)E, \\ L' = \lambda_2 + (1-p)\omega E - (d_L+\nu)L, \\ T' = p\omega E + \nu L - (d_T+\alpha+\delta+\gamma)T, \end{cases} \tag{B.2}$$

and the endemic equilibrium satisfies the following equations

$$\begin{cases} (\pi - d_X\delta/\beta) = \beta S^*T^* + d_X S^*, \\ \lambda_1 + \beta S^*T^* + (\delta+\gamma)T^* = (d_E+\omega)E^*, \\ \lambda_2 + (1-p)\omega E^* = (d_L+\nu)L^*, \\ p\omega E^* + \nu L^* = (d_T+\alpha+\delta+\gamma)T^*. \end{cases} \tag{B.3}$$

Let $\tilde{P}^* = (S^*, E^*, L^*, T^*)$ be the endemic equilibrium of model (B.2). Then for the endemic equilibrium P^* of (B.2), we have the following result.

Theorem B.1. *The system* (B.2) *always has a unique endemic equilibrium* $\tilde{P}^* = (S^*, E^*, L^*, T^*)$ *which is globally asymptotically stable in the reduced feasible region* Γ_r.

Proof: Set $x(t) = (S(t), E(t), L(t), T(t)) \in \Gamma_r \subset \mathbb{R}^4_+$. Consider the Lyapunov function

$$\begin{aligned} V(x) = V(S,E,L,T) &= A(S - S^* - S^*\ln\frac{S}{S^*}) + B(E - E^* - E^*\ln\frac{E}{E^*}) \\ &+ C(L - L^* - L^*\ln\frac{L}{L^*}) + D(T - T^* - T^*\ln\frac{T}{T^*}), \end{aligned}$$

where

$$A = B = \frac{(pd_L+\nu)\omega}{d_E+\omega},\ C = \nu,\ D = d_L+\nu, \tag{B.4}$$

are positive constants and (S^*, E^*, L^*, T^*) is the endemic equilibrium $\tilde{P}^*$. We note that the function $V(x)$ is positive definite with respect to $x^* = \tilde{P}^*$. The derivative of $V(t)$ along the solution $(S(t), E(t), L(t), T(t))$ is

$$V' = A(S' - \frac{S^*}{S}S') + B(E' - \frac{E^*}{E}E') + C(L' - \frac{L^*}{L}L') + D(T' - \frac{T^*}{T}T'). \tag{B.5}$$

Using system equations (B.2) and the first equation of (B.3), we could simplify

$$\begin{aligned} S' - \frac{S^*}{S}S' &= (\pi - d_X\delta/\beta) - \beta ST - d_X S - (\pi - d_X\delta/\beta)\frac{S^*}{S} + \beta S^*T + d_X S^* \\ &= (\beta S^*T^* + d_X S^*) - \beta ST - d_X S - (\beta S^*T^* + d_X S^*)\frac{S^*}{S} + \beta S^*T + d_X S^* \\ &= [\beta S^*T] - \beta ST + d_X S^*\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) + \beta S^*T^* - \frac{\beta S^*T^*S^*}{S} \\ &\le [\beta S^*T] - \beta ST + \beta S^*T^* - \frac{\beta S^*T^*S^*}{S}, \end{aligned} \tag{B.6}$$

since $2 - \frac{S}{S^*} - \frac{S^*}{S} \le 0$. Similarly, using (B.2), we have

$$\begin{aligned}
E' - \frac{E^*}{E}E' &= \lambda_1 + \beta ST + [(\delta+\gamma)T] - (d_E+\omega)E \\
&\quad -\frac{\lambda_1 E^*}{E} - \frac{\beta ST E^*}{E} - (\delta+\gamma)\frac{TE^*}{E} + (d_E+\omega)E^*, \\
L' - \frac{L^*}{L}L' &= \lambda_2 + [(1-p)\omega E - (d_L+\nu)L] \\
&\quad -\frac{\lambda_2 L^*}{L} - (1-p)\omega\frac{EL^*}{L} + (d_L+\nu)L^*, \\
T' - \frac{T^*}{T}T' &= [p\omega E + \nu L - (d_T+\alpha+\delta+\gamma)T] \\
&\quad -p\omega\frac{ET^*}{T} - \nu\frac{LT^*}{T} + (d_T+\alpha+\delta+\gamma)T^*.
\end{aligned} \tag{B.7}$$

Substitute (B.6), (B.7) into (B.5) and use (B.4), V' is rearranged as

$$\begin{aligned}
V' &= [A\beta S^* - A(\delta+\gamma) - D(d_T+\alpha+\gamma+\delta)]T \\
&\quad + \left[A\beta S^*T^* + A\lambda_1 + A(d_E+\omega)E^* + C\lambda_2 + C(d_L+\nu)L^* + D(d_T+\alpha+\gamma+\delta)T^*\right] \\
&\quad + \Big[-A\frac{\beta S^*T^*S^*}{S} - A\frac{\lambda_1 E^*}{E} - A\frac{\beta ST E^*}{E} - A\frac{(\delta+\gamma)TE^*}{E} \\
&\qquad - C\frac{\lambda_2 L^*}{L} - C\frac{(1-p)\omega EL^*}{L} - D\frac{p\omega ET^*}{T} - D\frac{\nu LT^*}{T}\Big] \\
&\doteq V_1 + V_2 + V_3.
\end{aligned} \tag{B.8}$$

Furthermore,

$$V_1 = A\beta S^* - A(\delta+\gamma) - D(d_T+\alpha+\gamma+\delta)]T = -[A\lambda_1 + \lambda_2\nu]\frac{T}{T^*}. \tag{B.9}$$

In fact we get it as follows. Combine the last two identities of (B.3) and cancel the L^* term

$$\lambda_2\nu + (pd_L+\nu)\omega E^* = (d_L+\nu)(d_T+\alpha+\delta+\gamma)T^*, \tag{B.10}$$

then combine (B.10) and the second equation of (B.3) and cancel the E^* term, we have

$$(pd_L+\nu)\omega[\lambda_1 + \beta S^*T^* + (\delta+\gamma)T^*] + \lambda_2\nu(d_E+\omega) = (d_E+\omega)(d_L+\nu)(d_T+\alpha+\delta+\gamma)T^*.$$

Divided by $(d_E+\omega)T^*$ both sides and use notations, we have

$$\frac{(pd_L+\nu)\omega}{(d_E+\omega)}\cdot\frac{\lambda_1 + \beta S^*T^* + (\delta+\gamma)T^*}{T^*} + \frac{\lambda_2\nu}{T^*} = (d_L+\nu)(d_T+\alpha+\delta+\gamma),$$

which is

$$A\frac{\lambda_1}{T^*} + A\beta S^* + A(\delta+\gamma) + \frac{\lambda_2\nu}{T^*} = D(d_T+\alpha+\delta+\gamma). \tag{B.11}$$

Rewrite (B.11) as

$$A\beta S^* + A(\delta+\gamma) - D(d_T+\alpha+\delta+\gamma) = -\frac{A\lambda_1}{T^*} - \frac{C\lambda_2}{T^*}. \tag{B.12}$$

For (B.12), times variable T both sides, which gives V_1.

Note that V_2 in (B.8) is a positive sum of constants. V_3 is the sum of negative nonlinear fraction term. Now we simplify the constant term V_2. Using (B.11) and the second and third endemic equilibrium equations of (B.3) and $C = \nu, D = d_L + \nu$, we could simplify V_2 as

$$\begin{aligned} V_2 &= 2A\beta S^*T^* + 2A\lambda_1 + A(\delta+\gamma)T^* + 2C\lambda_2 + A(d_E+\omega)E^* + C(d_L+\nu)L^* \\ &= 3A\beta S^*T^* + 3A\lambda_1 + 2A(\delta+\gamma)T^* + 2C\lambda_2 + C(d_L+\nu)L^* \\ &= 3A\beta S^*T^* + 3A\lambda_1 + 2A(\delta+\gamma)T^* + 3C\lambda_2 + (1-p)C\omega E^*. \end{aligned}$$

And note

$$\begin{aligned} (1-p)C\omega E^* &= \frac{(1-p)\nu}{pd_L+\nu}\frac{(pd_L+\nu)\omega}{d_E+\omega}(d_E+\omega)E^* \\ &= \frac{(1-p)\nu}{pd_L+\nu}A(d_E+\omega)E^* \\ &= \frac{(1-p)\nu}{pd_L+\nu}A[\beta S^*T^* + \lambda_1 + (\delta+\gamma)T^*], \end{aligned}$$

by the definition of A. Define

$$a_1 = \frac{p(d_L+\nu)}{pd_L+\nu}, \quad b_1 = \frac{(1-p)\nu}{pd_L+\nu}, \quad a_1+b_1 = 1, \quad a_1 > 0, \ b_1 > 0. \tag{B.13}$$

thus

$$\begin{aligned} V_2 &= 3A\beta S^*T^* + 3A\lambda_1 + 2A(\delta+\gamma)T^* + 3C\lambda_2 + Ab_1[\beta S^*T^* + \lambda_1 + (\delta+\gamma)T^*] \\ &= (3+b_1)[A\beta S^*T^* + A\lambda_1] + (2+b_1)A(\delta+\gamma)T^* + 3C\lambda_2 \\ &= (3a_1+4b_1)[A\beta S^*T^* + A\lambda_1] + (2a_1+3b_1)A(\delta+\gamma)T^* + 3C\lambda_2. \end{aligned}$$

Also note from the second endemic equilibrium equation of (B.3)

$$\lambda_1 + \beta S^*T^* + (\delta+\gamma)T^* = (d_E+\omega)E^*,$$

we define

$$\beta_1 = \frac{\lambda_1}{(d_E+\omega)E^*}, \ \beta_2 = \frac{\beta S^*T^*}{(d_E+\omega)E^*}, \ \beta_3 = \frac{(\delta+\gamma)T^*}{(d_E+\omega)E^*}, \tag{B.14}$$

thus $\beta_1+\beta_2+\beta_3=1$ and $\beta_i>0,\ i=1,2,3$. From the second and third endemic equilibrium equations of (B.3), canceling the E^* term, we get

$$\begin{aligned}\nu(d_L+\nu)L^* &= \frac{(1-p)\nu\omega}{(d_E+\omega)}[\lambda_1+\beta S^*T^*+(\delta+\gamma)T^*]+\lambda_2\nu \\ &= \frac{(1-p)\nu}{pd_L+\nu}\cdot\frac{(pd_L+\nu)\omega}{(d_E+\omega)}[\lambda_1+\beta S^*T^*+(\delta+\gamma)T^*]+\lambda_2\nu \\ &= b_1A[\lambda_1+\beta S^*T^*+(\delta+\gamma)T^*]+\lambda_2\nu.\end{aligned} \tag{B.15}$$

Define

$$\eta_1=\frac{b_1A\lambda_1}{\nu(d_L+\nu)L^*},\ \eta_2=\frac{b_1A\beta S^*T^*}{\nu(d_L+\nu)L^*},\ \eta_3=\frac{b_1A(\delta+\gamma)T^*}{\nu(d_L+\nu)L^*},\ \eta_4=\frac{\lambda_2\nu}{\nu(d_L+\nu)L^*}. \tag{B.16}$$

Here $\sum_{i=1}^4\eta_i=1$ and $\eta_i>0,\ i=1,2,3,4$. Now regrouping V_3 and V_1 in (B.9), we get

$$\begin{aligned}&V_1+V_3 \\ &= -A\frac{\beta S^*T^*S^*}{S}-A\frac{\lambda_1E^*}{E}-A\frac{\beta STE^*}{E}-A\frac{(\delta+\gamma)TE^*}{E}-C\frac{\lambda_2L^*}{L} \\ &-C\frac{(1-p)\omega EL^*}{L}-D\frac{p\omega ET^*}{T}-D\frac{\nu LT^*}{T}-A\frac{\lambda_1T}{T^*}-\frac{\lambda_2\nu T}{T^*} \\ &= -A(a_1+b_1)\frac{\beta S^*T^*S^*}{S}-A(a_1+b_1)\frac{\lambda_1E^*}{E}-A(a_1+b_1)\frac{\beta STE^*}{E} \\ &-A(a_1+b_1)\frac{(\delta+\gamma)TE^*}{E}-C\frac{\lambda_2L^*}{L}-C(\beta_1+\beta_2+\beta_3)\frac{(1-p)\omega EL^*}{L} \\ &-D(\beta_1+\beta_2+\beta_3)\frac{p\omega ET^*}{T}-D(\eta_1+\eta_2+\eta_3+\eta_4)\frac{\nu LT^*}{T}-A(a_1+b_1)\frac{\lambda_1T}{T^*}-\frac{\lambda_2\nu T}{T^*} \\ &= \left\{-Ab_1\frac{\beta S^*T^*S^*}{S}-Ab_1\frac{\beta STE^*}{E}-C\beta_2\frac{(1-p)\omega EL^*}{L}-D\eta_2\frac{\nu LT^*}{T}\right\} \\ &+\left\{-Aa_1\frac{\beta S^*T^*S^*}{S}-Aa_1\frac{\beta STE^*}{E}-D\beta_2\frac{p\omega ET^*}{T}\right\} \\ &+\left\{-Aa_1\frac{(\delta+\gamma)TE^*}{E}-D\beta_3\frac{p\omega ET^*}{T}\right\} \\ &+\left\{-Ab_1(\delta+\gamma)\frac{TE^*}{E}-C\beta_3\frac{(1-p)\omega EL^*}{L}-D\eta_3\frac{\nu LT^*}{T}\right\} \\ &+\left\{-Ab_1\frac{\lambda_1E^*}{E}-Ab_1\frac{\lambda_1T}{T^*}-C\beta_1\frac{(1-p)\omega EL^*}{L}-D\eta_1\frac{\nu LT^*}{T}\right\} \\ &+\left\{-Aa_1\frac{\lambda_1E^*}{E}-Aa_1\frac{\lambda_1T}{T^*}-D\beta_1\frac{p\omega ET^*}{T}\right\} \\ &+\left\{-\frac{\lambda_2\nu T}{T^*}-C\frac{\lambda_2L^*}{L}-D\eta_4\frac{\nu LT^*}{T}\right\} \\ &\doteq I_1+I_2+I_3+I_4+I_5+I_6+I_7.\end{aligned} \tag{B.17}$$

Combine V_1, V_2 and V_3, we have

$$\begin{aligned}\frac{dV}{dt} &= V_2 + V_3 + V_1 \\ &= (3a_1 + 4b_1)(A\beta S^* T^* + A\lambda_1) + 3C\lambda_2 + (2a_1 + 3b_1)A(\delta + \gamma)T^* + \sum_{i=1}^{7} I_i \\ &= [4b_1 A\beta S^* T^* + I_1] + [3a_1 A\beta S^* T^* + I_2] \\ &+ [2a_1 A(\delta + \gamma)T^* + I_3] + [3b_1 A(\delta + \gamma)T^* + I_4] \\ &+ [4b_1 A\lambda_1 + I_5] + [3a_1 A\lambda_1 + I_6] + [3C\lambda_2 + I_7].\end{aligned} \tag{B.18}$$

Applying the inequality

$$\frac{x_1 + x_2 + \cdots + x_n}{n} \geq \sqrt[n]{x_1 \cdot x_2 \cdots x_n}, \quad (x_i \geq 0, i = 1, 2, \cdots, n),$$

we want to show that $V_2 + V_1 + V_3 \leq 0$. Using the definition of A, C, D, (B.13), (B.14), (B.16), we obtain the following group of inequalities.

$$\begin{aligned}&4b_1 A\beta S^* T^* + I_1 \\ &\leq 4b_1 A\beta S^* T^* - 4\sqrt[4]{Ab_1\beta S^* T^* S^* \cdot Ab_1\beta E^* \cdot C\beta_2(1-p)\omega L^* \cdot D\eta_2\nu T^*} \\ &= 4b_1 A\beta S^* T^* - 4\sqrt[4]{(Ab_1\beta S^* T^*)^2 \cdot (1-p)C\omega \cdot \beta_2 E^* \cdot D\nu\eta_2 L^*} \\ &= 4b_1 A\beta S^* T^* - 4\sqrt[4]{(Ab_1\beta S^* T^*)^2 \frac{(1-p)\nu}{pd_L + \nu}\frac{(pd_L + \nu)\omega}{d_E + \omega}\beta_2(d_E + \omega)E^* \; D\nu\eta_2 L^*} \\ &= 4b_1 A\beta S^* T^* - 4\sqrt[4]{(Ab_1\beta S^* T^*)^2 \cdot b_1 \cdot A \cdot \beta S^* T^* \cdot b_1 A\beta S^* T^*} \\ &= 0.\end{aligned} \tag{B.19}$$

Similarly we have

$$\begin{aligned}&3a_1 A\beta S^* T^* + I_2 \\ &\leq 3a_1 A\beta S^* T^* - 3\sqrt[3]{Aa_1\beta S^* T^* S^* \cdot Aa_1\beta E^* \cdot D\beta_2 p\omega T^*} \\ &= 3a_1 A\beta S^* T^* - 3\sqrt[3]{[Aa_1\beta S^* T^*]^2 \cdot pD\omega \cdot \beta_2 E^*} \\ &= 3a_1 A\beta S^* T^* - 3\sqrt[3]{[Aa_1\beta S^* T^*]^2 \cdot \frac{p(d_L + \nu)}{pd_L + \nu} \cdot \frac{(pd_L + \nu)\omega}{d_E + \omega} \cdot \beta_2(d_E + \omega)E^*} \\ &= 3a_1 A\beta S^* T^* - 3\sqrt[3]{[Aa_1\beta S^* T^*]^2 \cdot a_1 \cdot A \cdot \beta S^* T^*} \\ &= 0.\end{aligned} \tag{B.20}$$

$$
\begin{aligned}
&2a_1A(\delta+\gamma)T^* + I_3 \\
&\le 2a_1A(\delta+\gamma)T^* - 2\sqrt{Aa_1(\delta+\gamma)E^* \cdot D\beta_3 p\omega T^*} \\
&= 2a_1A(\delta+\gamma)T^* - 2\sqrt{Aa_1(\delta+\gamma)T^* \cdot pD\omega \cdot \beta_3 E^*} \\
&= 2a_1A(\delta+\gamma)T^* - 2\sqrt{Aa_1(\delta+\gamma)T^* \cdot \frac{p(d_L+\nu)}{pd_L+\nu} \cdot \frac{(pd_L+\nu)\omega}{d_E+\omega} \cdot \beta_3(d_E+\omega)E^*} \\
&= 2a_1A(\delta+\gamma)T^* - 2\sqrt{Aa_1(\delta+\gamma)T^* \cdot a_1 \cdot A \cdot (\delta+\gamma)T^*} \\
&= 0.
\end{aligned} \tag{B.21}
$$

$$
\begin{aligned}
&3b_1A(\delta+\gamma)T^* + I_4 \\
&\le 3b_1A(\delta+\gamma)T^* - 3\sqrt[3]{Ab_1(\delta+\gamma)E^* \cdot C\beta_3(1-p)\omega L^* \cdot D\eta_3\nu T^*} \\
&= 3b_1A(\delta+\gamma)T^* - 3\sqrt[3]{Ab_1(\delta+\gamma)T^* \cdot (1-p)C\omega \cdot \beta_3 E^* \cdot D\nu\eta_3 L^*} \\
&= 3b_1A(\delta+\gamma)T^* - 3\sqrt[3]{Ab_1(\delta+\gamma)T^* \frac{(1-p)\nu}{pd_L+\nu}\frac{(pd_L+\nu)\omega}{d_E+\omega}\beta_3(d_E+\omega)E^* D\nu\eta_3 L^*} \\
&= 3b_1A(\delta+\gamma)T^* - 3\sqrt[3]{Ab_1(\delta+\gamma)T^* \cdot b_1 \cdot A \cdot (\delta+\gamma)T^* \cdot b_1A(\delta+\gamma)T^*} \\
&= 0.
\end{aligned} \tag{B.22}
$$

$$
\begin{aligned}
&4b_1A\lambda_1 + I_5 \\
&\le 4b_1A\lambda_1 - 4\sqrt[4]{Ab_1\lambda_1E^* \cdot Ab_1\lambda_1 \cdot D\eta_1\nu \cdot C\beta_1(1-p)\omega L^*} \\
&= 4b_1A\lambda_1 - 4\sqrt[4]{(Ab_1\lambda_1)^2 \cdot (1-p)C\omega \cdot \beta_1 E^* \cdot D\eta_1\nu L^*} \\
&= 4b_1A\lambda_1 - 4\sqrt[4]{(Ab_1\lambda_1)^2 \cdot \frac{(1-p)\nu}{pd_L+\nu} \cdot \frac{(pd_L+\nu)\omega}{d_E+\omega} \cdot \beta_1(d_E+\omega)E^* \cdot \eta_1 D\nu L^*} \\
&= 4b_1A\lambda_1 - 4\sqrt[4]{(Ab_1\lambda_1)^2 \cdot b_1 \cdot A \cdot \lambda_1 \cdot Ab_1\lambda_1} \\
&= 0.
\end{aligned} \tag{B.23}
$$

$$
\begin{aligned}
&3a_1A\lambda_1 + I_6 \\
&\le 3a_1A\lambda_1 - 3\sqrt[3]{Aa_1\lambda_1E^* \cdot Aa_1\lambda_1 \cdot D\beta_1 p\omega} \\
&= 3a_1A\lambda_1 - 3\sqrt[3]{(Aa_1\lambda_1)^2 \cdot pD\omega \cdot \beta_1 E^*} \\
&= 3a_1A\lambda_1 - 3\sqrt[3]{(Aa_1\lambda_1)^2 \cdot \frac{p(d_L+\nu)}{pd_L+\nu} \cdot \frac{(pd_L+\nu)\omega}{d_E+\omega} \cdot \beta_1(d_E+\omega)E^*} \\
&= 3a_1A\lambda_1 - 3\sqrt[3]{(Aa_1\lambda_1)^2 \cdot a_1 \cdot A \cdot \lambda_1} \\
&= 0.
\end{aligned} \tag{B.24}
$$

$$
\begin{aligned}
3C\lambda_2 + I_7 &\leq 3C\lambda_2 - 3\sqrt[3]{C\lambda_2 L^* \cdot \lambda_2 \nu \cdot D\eta_4 \nu} \\
&= 3C\lambda_2 - 3\sqrt[3]{(C\lambda_2)^2 \cdot \eta_4 D\nu L^*} \\
&= 3C\lambda_2 - 3\sqrt[3]{(C\lambda_2)^2 \cdot C\lambda_2} \\
&= 0.
\end{aligned} \tag{B.25}
$$

Substitute (B.19)-(B.25) into (B.18), we obtain that $V_2 + V_3 \leq 0$ and thus

$$
\frac{dV}{dt} = V_1 + V_2 + V_3 \leq 0. \tag{B.26}
$$

Furthermore, $\frac{dV}{dt} = 0$ if and only if equalities hold in (B.19)-(B.25). Therefore $\frac{dV}{dt}$ is negative definite in Int Γ with respect to the endemic equilibrium $x^* = \bar{P}^*$. This implies that the basin of attraction of $\bar{P}^*$ contains the interior of Γ. The positive definiteness of $V(x)$ with respect to $\bar{P}^*$ implies that $\bar{P}^*$ is also locally stable. This completes the proof.

Another proof using the graph-theoretical approach

We can simplify the proof of GAS of P^* using the graph-theoretical approach we developed in Chapter 1.

From (B.3) we have

$$
A\beta S^* T^* + B\lambda_1 + B(\delta + \gamma)T^* + C\lambda_2 = D(d_T + \alpha + \delta + \gamma)T^*, \tag{B.27}
$$

where A, B, C, D are defined in (B.4). From (B.6) and (B.7) we want the following always hold:

$$
\begin{aligned}
0 &= [-A + B]\beta ST, \\
0 &= [C(1-p)\omega + Dp\omega - B(d_E + \omega)]E, \\
0 &= [D\nu - C(d_L + \nu)]L.
\end{aligned} \tag{B.28}
$$

for all values of S, E, L, T. And it is also true for S^*, E^*, L^*, T^*. Then (B.28) becomes

$$
\begin{aligned}
A\beta S^* T^* &= B\beta S^* T^*, \\
C(1-p)\omega E^* + Dp\omega E^* &= B(d_E + \omega)]E^*, \\
D\nu L^* &= C(d_L + \nu)L^*.
\end{aligned} \tag{B.29}
$$

Multiply B, C, D both sides at the last three identities in (B.3), we have

$$
\begin{cases}
B\lambda_1 + B\beta S^* T^* + B(\delta + \gamma)T^* = B(d_E + \omega)E^*, \\
C\lambda_2 + C(1-p)\omega E^* = C(d_L + \nu)L^*, \\
Dp\omega E^* + D\nu L^* = D(d_T + \alpha + \delta + \gamma)T^*.
\end{cases} \tag{B.30}
$$

Use (B.30), (B.28) and (B.29), we have

$$\begin{cases} A\beta S^*T^* = B\beta S^*T^*, \\ B\lambda_1 + B\beta S^*T^* + B(\delta+\gamma)T^* = C(1-p)\omega E^* + Dp\omega E^*, \\ C\lambda_2 + C(1-p)\omega E^* = D\nu L^*, \\ A\beta S^*T^* + B\lambda_1 + B(\delta+\gamma)T^* + C\lambda_2 = Dp\omega E^* + D\nu L^*. \end{cases} \tag{B.31}$$

Consider A, B, C, D are variables, we get a linear system

$$\begin{bmatrix} \beta S^*T^* & -\beta S^*T^* & 0 & 0 \\ 0 & \lambda_1 + \beta S^*T^* + (\delta+\gamma)T^* & -(1-p)\omega E^* & -p\omega E^* \\ 0 & 0 & \lambda_2 + (1-p)\omega E^* & -\nu L^* \\ -\beta S^*T^* & -\lambda_1 - (\delta+\gamma)T^* & -\lambda_2 & p\omega E^* + \nu L^* \end{bmatrix} \begin{bmatrix} A \\ B \\ C \\ D \end{bmatrix} = 0. \tag{B.32}$$

Solving (B.32), we have

$$\begin{aligned} A &= \beta S^*T^* \cdot \omega E^* \cdot [(1-p)p\omega E^* + p\lambda_2 + (1-p)\nu L^*], \\ B &= \beta S^*T^* \cdot \omega E^* \cdot [(1-p)p\omega E^* + p\lambda_2 + (1-p)\nu L^*], \\ C &= \beta S^*T^* \cdot \nu L^* \cdot [\lambda_1 + \beta S^*T^* + (\delta+\gamma)T^*], \\ D &= \beta S^*T^* \cdot [\lambda_2 + (1-p)\omega E^*][\lambda_1 + \beta S^*T^* + (\delta+\gamma)T^*]. \end{aligned} \tag{B.33}$$

Using (B.9), (B.8) becomes

$$\begin{aligned} V' = &\Big[A\beta S^*T^* + A\lambda_1 + A(d_E+\omega)E^* + C\lambda_2 + C(d_L+\nu)L^* + D(d_T+\alpha+\gamma+\delta)T^*\Big] \\ &+ \Big[- A\frac{\beta S^*T^*S^*}{S} - A\frac{\lambda_1 E^*}{E} - A\frac{\beta STE^*}{E} - A\frac{(\delta+\gamma)TE^*}{E} - A\lambda_1\frac{T}{T^*} \\ &- \lambda_2 C\frac{T}{T^*} - C\frac{\lambda_2 L^*}{L} - C\frac{(1-p)\omega EL^*}{L} - D\frac{p\omega ET^*}{T} - D\frac{\nu LT^*}{T}\Big]. \end{aligned} \tag{B.34}$$

Use the last three identities in (B.3), (B.34) becomes

$$
\begin{aligned}
V' &= 2A\beta S^*T^* + 2A\lambda_1 + A(\delta+\gamma)T^* + 2C\lambda_2 + C(1-p)\omega E^* + Dp\omega E^* + D\nu L^* \\
&- A\beta S^*T^*\frac{S^*}{S} - A\lambda_1\frac{E^*}{E} - A\beta S^*T^*\frac{S}{S^*}\frac{T}{T^*}\frac{E^*}{E} - A(\delta+\gamma)T^*\frac{T}{T^*}\frac{E^*}{E} - A\lambda_1\frac{T}{T^*} \\
&- C\lambda_2\frac{T}{T^*} - C\lambda_2\frac{L^*}{L} - C(1-p)\omega E^*\frac{E}{E^*}\frac{L^*}{L} - Dp\omega E^*\frac{E}{E^*}\frac{T^*}{T} - D\nu L^*\frac{L}{L^*}\frac{T^*}{T} \\
&= A\beta S^*T^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\frac{T}{T^*}\frac{E^*}{E}\right) + A\lambda_1\left(2 - \frac{E^*}{E} - \frac{T}{T^*}\right) \\
&+ A(\delta+\gamma)T^*\left(1 - \frac{T}{T^*}\frac{E^*}{E}\right) + C\lambda_2\left(2 - \frac{T}{T^*} - \frac{L^*}{L}\right) + D\nu L^*\left(1 - \frac{L}{L^*}\frac{T^*}{T}\right) \\
&+ C(1-p)\omega E^*\left(1 - \frac{E}{E^*}\frac{L^*}{L}\right) + Dp\omega E^*\left(1 - \frac{E}{E^*}\frac{T^*}{T}\right).
\end{aligned}
\tag{B.35}
$$

Note coefficients in each term in (B.35) can be regrouped as

$$
\begin{aligned}
A\lambda_1 &= \beta S^*T^* \cdot p\omega E^* \cdot \lambda_1 \cdot [\lambda_2 + (1-p)\omega E^*] \\
&+ \beta S^*T^* \cdot (1-p)\omega E^* \cdot \lambda_1 \cdot \nu L^*, \\
A\beta S^*T^* &= (\beta S^*T^*)^2 \cdot p\omega E^* \cdot [\lambda_2 + (1-p)\omega E^*] \\
&+ (\beta S^*T^*)^2 \cdot (1-p)\omega E^* \cdot \nu L^*, \\
A(\delta+\gamma)T^* &= \beta S^*T^* \cdot p\omega E^* \cdot (\delta+\gamma)T^* \cdot [\lambda_2 + (1-p)\omega E^*] \\
&+ \beta S^*T^* \cdot (1-p)\omega E^* \cdot \nu L^* \cdot (\delta+\gamma)T^*.
\end{aligned}
\tag{B.36}
$$

$$
\begin{aligned}
C\lambda_2 &= \beta S^*T^* \cdot \nu L^* \cdot \lambda_2 \cdot [\lambda_1 + \beta S^*T^* + (\delta+\gamma)T^*], \\
C(1-p)\omega E^* &= (\beta S^*T^*)^2 \cdot \nu L^* \cdot (1-p)\omega E^* \\
&+ \beta S^*T^* \cdot \nu L^* \cdot \lambda_1 \cdot (1-p)\omega E^* \\
&+ \beta S^*T^* \cdot \nu L^* \cdot (\delta+\gamma)T^* \cdot (1-p)\omega E^*.
\end{aligned}
\tag{B.37}
$$

$$
\begin{aligned}
D\nu L^* &= \beta S^*T^* \cdot \nu L^* \cdot \lambda_2 \cdot [\lambda_1 + \beta S^*T^* + (\delta+\gamma)T^*] \\
&+ (\beta S^*T^*)^2 \cdot \nu L^* \cdot (1-p)\omega E^* \\
&+ \beta S^*T^* \cdot \nu L^* \cdot (1-p)\omega E^* \cdot \lambda_1 \\
&+ \beta S^*T^* \cdot \nu L^* \cdot (1-p)\omega E^* \cdot (\delta+\gamma)T^*, \\
Dp\omega E^* &= (\beta S^*T^*)^2 \cdot p\omega E^* \cdot [\lambda_2 + (1-p)\omega E^*] \\
&+ \beta S^*T^* \cdot p\omega E^* \cdot \lambda_1 \cdot [\lambda_2 + (1-p)\omega E^*] \\
&+ \beta S^*T^* \cdot p\omega E^* \cdot (\delta+\gamma)T^* \cdot [\lambda_2 + (1-p)\omega E^*].
\end{aligned}
\tag{B.38}
$$

Then we can combine all terms with the same coefficients (expanded in (B.36), (B.37), (B.38)) into one group

$$
\begin{aligned}
V' \leq\ & (\beta S^* T^*)^2 \cdot p\omega E^* \cdot [\lambda_2 + (1-p)\omega E^*] \left(3 - \frac{S^*}{S} - \frac{S}{S^*}\frac{T}{T^*}\frac{E^*}{E} - \frac{E}{E^*}\frac{T^*}{T}\right) \\
& + (\beta S^* T^*)^2 \cdot (1-p)\omega E^* \cdot \nu L^* \left(4 - \frac{S^*}{S} - \frac{S}{S^*}\frac{T}{T^*}\frac{E^*}{E} - \frac{L}{L^*}\frac{T^*}{T} - \frac{E}{E^*}\frac{L^*}{L}\right) \\
& + \beta S^* T^* \cdot p\omega E^* \cdot (\delta+\gamma) T^* \cdot [\lambda_2 + (1-p)\omega E^*] \left(2 - \frac{T}{T^*}\frac{E^*}{E} - \frac{E}{E^*}\frac{T^*}{T}\right) \\
& + \beta S^* T^* \cdot p\omega E^* \cdot \lambda_1 \cdot [\lambda_2 + (1-p)\omega E^*] \left(3 - \frac{E^*}{E} - \frac{T}{T^*} - \frac{E}{E^*}\frac{T^*}{T}\right) \\
& + (\beta S^* T^*)^2 \cdot (1-p)\omega E^* \cdot \nu L^* \left(4 - \frac{E^*}{E} - \frac{T}{T^*} - \frac{L}{L^*}\frac{T^*}{T} - \frac{E}{E^*}\frac{L^*}{L}\right) \\
& + \beta S^* T^* \cdot \nu L^* \cdot \lambda_2 \cdot [\lambda_1 + \beta S^* T^* + (\delta+\gamma) T^*] \left(3 - \frac{T}{T^*} - \frac{L^*}{L} - \frac{L}{L^*}\frac{T^*}{T}\right) \\
& + \beta S^* T^* \cdot (1-p)\omega E^* \cdot \nu L^* \cdot (\delta+\gamma) T^* \left(4 - \frac{L}{L^*}\frac{T^*}{T} - \frac{E}{E^*}\frac{L^*}{L} - \frac{T}{T^*}\frac{E^*}{E}\right) \\
& \leq 0,
\end{aligned}
\tag{B.39}
$$

by applying the inequality seven times

$$
\frac{x_1 + x_2 + \cdots + x_n}{n} \geq \sqrt[n]{x_1 \cdot x_2 \cdots x_n}, \quad (x_i \geq 0, i = 1, 2, \cdots, n).
$$

The results are same as that in (B.19)-(B.25).

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